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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL
515(i) RECLASSIFICATION PANEL

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September 12, 2013
8:00 a.m.

Hilton Washington, D.C. North
620 Perry Parkway
Gaithersburg, Maryland

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RICHARD L. PAGE, M.D.	Temporary Panel Chair
JOHN C. SOMBERG, M.D.	Voting Member
RICHARD A. LANGE, M.D.	Voting Member
E. MAGNUS OHMAN, M.B., FRCPI, FACC	Voting Member
DAVID D. YUH, M.D.	Voting Member
DAVID C. NAFTEL, Ph.D.	Voting Member
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JONATHAN D. REICH, M.D., M.Sc.	Temporary Non-Voting Member
DAVID T. BALZER, M.D.	Temporary Non-Voting Member
JUDITH CURRIER	Patient Representative
SHARON TIMBERLAKE, M.S.H.S., RAC, CCRA	Industry Representative
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M E E T I N G

(8:04 a.m.)

DR. PAGE: Call this meeting of the Circulatory System Devices Panel to order. I'm Dr. Richard Page. I'm Chair of Medicine at the University of Wisconsin, and my area of expertise is clinical cardiac electrophysiology. And I welcome the Panel, who will be introducing themselves in a few moments.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in this meeting today has received training in FDA device law and regulations.

For today's agenda, the Committee will discuss and make recommendations regarding the proposed classification of membrane lung for long-term pulmonary support systems, one of the remaining preamendment Class III devices regulated under the 510(k) pathway.

A membrane lung for long-term pulmonary support refers to the oxygenator component of an extracorporeal circuit used during long-term procedures, commonly referred to as ECMO.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. And if I may, I'll start with Ms. Timberlake.

MS. TIMBERLAKE: Good morning. My name is Sharon Timberlake. I am the Industry Representative. I'm employed by OmniGuide Surgical. I've been in the medical device for over 18 years in the areas of clinical, quality, and regulatory affairs.

MS. MATTIVI: Good morning. I'm Kris Mattivi, physical therapist and manager of analytic services at the Colorado Foundation for Medical Care, the Medicare Quality Improvement Organization for the state of Colorado. And I am the Consumer Representative to the Panel.

DR. BORER: My name is Jeff Borer. I'm a cardiologist. I'm former Chairman of Medicine at the State University of New York and currently the Chairman of Cardiovascular Medicine at the State University of New York in New York City, and Professor of Medicine, Surgery, Cell Biology and Radiology at that institution.

DR. SLOTWINER: Good morning. My name is David Slotwiner. I'm a clinical cardiac electrophysiologist, and I practice at North Shore-Long Island Jewish Medical Center, Hofstra School of Medicine.

DR. REICH: Good morning. My name is Dr. Jonathan Reich. I'm a pediatric cardiologist in private practice. I'm also a biomedical engineer. I teach engineering at the University of South Florida, School of Engineering in Tampa, and I'm on faculty at Florida Atlantic University Medical School in Boca Raton, Florida.

DR. NAFTEL: Good morning. My name's David Naftel. I'm a

Professor of Surgery and Professor of Biostatistics at the University of Alabama at Birmingham, and my area is statistics.

DR. LANGE: My name is Rick Lange. My background is in interventional cardiology, and I'm currently Professor and Executive Vice Chairman of the Department of Medicine at the University of Texas in San Antonio.

MS. WATERHOUSE: Jamie Waterhouse. I'm the Designated Federal Officer for FDA.

DR. OHMAN: Good morning. I'm Magnus Ohman, interventional cardiologist at Duke in North Carolina. I'm a specialist in interventional high-risk procedures, as well as the issue of clinical trials at Duke Clinical Research Institute.

DR. YUH: Good morning. My name is David Yuh. I'm the Chief of Cardiac Surgery at Yale University. My areas of interest are in less invasive approaches to cardiac surgery and computational modeling of the heart.

DR. SOMBERG: My name is John Somberg. I'm a Professor of Medicine and Pharmacology at Rush University in Chicago.

DR. JAQUISS: My name is Jake Jaquiss. I'm a pediatric cardiac surgeon at Duke, with a particular interest in neonatal cardiac surgery and mechanical circulatory support in children.

DR. BALZER: David Balzer. I'm a Professor of Pediatrics and an interventional pediatric cardiologist at Washington University in St. Louis.

DR. CIGARROA: Good morning. I'm Joaquin Cigarroa. I'm an interventional cardiologist, Clinical Professor of Medicine at Oregon Health and Science University, and the Clinical Chief of the Knight Cardiovascular Institute.

DR. ALLEN: My name is Keith Allen. I'm Director of Surgical Research at the Mid-America Heart Institute in Kansas City, Missouri. I'm a cardiothoracic and vascular surgeon active in our adult transplant VAD and ECMO programs.

MS. CURRIER: Good morning. I'm Judy Currier. I am the Patient Representative. And my background is in systems analysis and mathematics.

DR. ZUCKERMAN: And Bram Zuckerman, Director, FDA Division of Cardiovascular Devices. Good morning.

DR. PAGE: Thank you very much.

As you can see, we have a truly expert Panel. A number of us did a Panel yesterday. This is a seasoned group, and we welcome the specialists in pediatrics, especially today, to round out this expert Panel.

If you've not already done so, please sign the attendance sheets. They're on the table by the doors.

Ms. Waterhouse, the Designated Federal Officer for the Circulatory System Devices Panel, will now make some introductory remarks.

MS. WATERHOUSE: The Food and Drug Administration is

convening today's meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S. Code 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflicts of interest.

Related to the discussions of today's meeting, members and consultants of this Panel have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S. Code Section 208, their employers. These interests may include investments; consulting; expert

witness testimony; contracts/grants/CRADAs; teaching/speaking/ writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations regarding the proposed classification of membrane lung for long-term pulmonary support systems, commonly referred to as extracorporeal membrane oxygenation, ECMO, to either reconfirm to Class III or reclassify to Class II. The Panel will also comment on whether special controls are adequate to reasonably ensure the safety and effectiveness of this device. ECMO is intended for patients with acute reversible respiratory or cardiac failure, unresponsive to optimal ventilation and/or pharmacologic management. The agenda for this meeting is classified as a particular matter of general applicability.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S. Code Section 208.

Sharon Timberlake is serving as the Industry Representative, acting on behalf of related industry, and is employed by OmniGuide Surgical.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their

exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Before I turn the meeting back over to Dr. Miller, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting. Their telephone is 410-974-0947. Information on purchasing videos of today's meeting can be found at the FDA meeting registration desk.

The press contact for today's meeting is Susan Laine.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is in the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing Session today and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please

be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time. Thank you.

DR. PAGE: Thank you, Ms. Waterhouse.

Before we get started, I'd like to just remind the Panel of a couple of the ground rules here. And one is that everything you have to say is really important to the Panel and to the process, and as such, I ask that there be no side conversations, that all statements be into a microphone that's turned off after you've been called on, and that way, we'll be able to take advantage of the expertise here in the room.

I'd also like to remind you that all of our conversations during this day until we adjourn regarding the subject at hand need to take place in this setting, in an open public meeting, and as such, during breaks and lunch, we will not discuss the matters at hand.

Finally, this room is unusual in terms of acoustics. And one of the problems with acoustics has to do with microphones being on. Actually, when we turn on our microphone, it turns off some speakers. So I will be asking people to make sure to turn off their microphones. And if your little light is on, I'll just be asking you to make sure you turn off your microphone. That'll actually improve the acoustics and allow us to hear everybody's important comments during the day.

We'll proceed now and hear from Marjorie Shulman, M.B.A.,

Director of Premarket Notification or the 510(k) program. I'd like to remind public observers that, while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

Ms. Shulman?

MS. SHULMAN: Good morning. Setting up the slides again. Wouldn't be me if it was all ready. Do I have to do something? I see them right here, I swear. They're right here.

DR. PAGE: Once more to give it back to you as well.

MS. SHULMAN: Thank you.

All right. Good morning. I'm Marjorie Shulman, Director of the Premarket Notification Program. And I'm going to go over some basic rules and regulations of why we're here today.

So the purpose of the Panel meeting today is to provide input to the FDA on the classification of preamendment device types and whether FDA should call for PMAs or reclassify to Class II or Class I. It's also to provide input to the FDA on the -- yesterday was to provide input on a preamendment device.

So what is a preamendment or a postamendment device? A preamendment device is a device that was introduced into interstate commerce prior to May 28th, 1976, the enactment date of the Medical Device Amendments. Postamendment devices were devices that were not in

commercial distribution prior to that date.

So recent legislation, FDASIA, has affected the classification of medical devices, including Class III 510(k)s, and FDA must now publish a proposed order announcing our proposed classification and seek public comment, hold a Panel meeting if classifying or reclassifying a device type, consider comments and all available information, including Panel recommendations, prior to issuing a final order finalizing the classification of the device type.

So the three classes are Class I, II, and III. The classification is based on the controls necessary, and a device should be placed in the lowest class whose level of control provides reasonable assurance of safety and effectiveness. There's Class I (general controls), Class II (general and special controls), and Class III (premarket approval).

General controls include prohibition against adulterated or misbranded devices, good manufacturing practices, registration of the manufacturing facility, listing of the device type, and recordkeeping, et cetera.

Special controls include performance standards, postmarket surveillance, patient registries, and development and dissemination of guidelines, et cetera.

There's also Class I devices is for devices for which general controls are sufficient to provide reasonable assurance of the safety and

effectiveness. And Class I devices typically require no 510(k) premarket review prior to being marketed. And many Class I devices are also typically exempt from many quality system control requirements, such as design controls. Class I devices is also a category for devices that cannot be classified into Class III because they are not life sustaining and life supporting, of substantial importance in preventing impairment of public health, and because they do not present an unreasonable risk of illness or injury. And they can't be classified into Class II because insufficient information exists to establish special controls to provide reasonable assurance of safety and effectiveness.

Some examples of Class I devices include such things as general cardiovascular surgical instruments, adhesive bandages, manual stethoscopes, and crutches.

Class II is for devices that can't be classified into Class I because the general controls are insufficient to provide reasonable assurance of the safety and effectiveness of the device and for which there is sufficient information to establish special controls to provide such assurance. Class II devices typically require premarket notification, also known as 510(k), to FDA prior to being marketed.

Examples of Class II devices include such things as blood pressure cuffs, percutaneous catheters, electronic stethoscopes, vascular graft prosthesis, ECGs, hemodialysis system, and syringes.

So special controls, how are they used? As an example, PTCA catheters were reclassified from Class III to Class II under special controls. FDA issued a special controls guidance to mitigate the risks to health, which included such things as biocompatibility testing, bench testing, animal testing, sterility, and shelf life. Also, such things as, in the labeling, warnings, precautions, adverse events, et cetera. These special controls, in combination with the general controls, provide reasonable assurance of the safety and effectiveness. Companies must provide evidence in their 510(k) submission of how the special controls were addressed.

Class III is for devices that cannot be classified into Class II because insufficient information exists to determine that the general and the special controls are sufficient to provide reasonable assurance of the safety and effectiveness, and the devices are life sustaining and/or life supporting, or are of substantial importance in preventing impairment of human health, or present an unreasonable risk of illness or injury. Class III devices typically require premarket approval, also known as PMA, prior to being marketed.

Some examples of Class III devices are endovascular grafts, coronary and peripheral stents, percutaneous heart valves, LVADs, cardiac occluders, and implantable pacemakers.

So what are Class III 510(k) devices? Those were preamendment devices, which FDA issued a proposed rule classifying them into Class III; however, no final rule was issued, or a final rule was issued for

Class III, but the rule did not contain a date by which companies were required to submit a PMA. Therefore, these Class III devices are allowed to proceed to market via the 510(k) process until such time as either a call for PMAs or a reclassification is finalized.

So FDA may reclassify a preamendment device in a proceeding that paralleled the initial classification proceeding based upon new information respecting a device either on FDA's own initiative or upon the petition of an interested person. The industry classifies or reclassifies the intended uses which have actually been reviewed by the agency.

So FDA may reclassify a postamendment device based upon new information respecting a device either on FDA's own initiative or upon the petition of an interested person if sufficient regulatory control exists to provide reasonable assurance of safety and effectiveness. We may consult with an advisory committee if needed. And the Agency reclassifies intended uses that have actually been reviewed by the Agency.

So here is a little flowchart for you that shows if general controls are sufficient for the device, it can go into Class I. If general controls are not sufficient, but there is sufficient information for -- to establish special controls, it can go into Class II. If that is not -- if there's not sufficient information for that and it's life sustaining and life supporting and of substantial importance to human health and presents an unreasonable risk of illness or injury, it can go into Class III. And the other road, if all those are no,

it can go into Class I.

So what do we need from the Panel? We need input on the classification of the device that's the subject of the Panel session today. The input should include identification of the risks to health, if any, presented by the device; whether the device is life supporting and life sustaining, of substantial importance in preventing impairment to human health, or presents a potential unreasonable risk of illness or injury; whether sufficient information exists to develop special controls; the identification of those special controls; and whether general controls alone are sufficient.

After the Panel meeting, FDA will consider the available evidence, including the input of this Panel and the public comments. FDA will issue a proposed order proposing the classification of the device and seeking public comment, or the reclassification of the device. FDA may propose that the device type be reclassified or remain in Class III, in which case we would call for PMAs, premarket approval applications, or split the classification based on indications or technology.

FDA will issue a final order identifying the appropriate class. If Class I or II, devices may continue to be marketed. If Class III, existing devices will remain on the market, but must submit a PMA by a specified time to continue marketing. If the PMA is not approved, devices will be considered misbranded and must be removed from commercial distribution.

FDA will consider the available evidence, including the input of

this Panel and public comments. If FDA believes the device can be reclassified, FDA will propose reclassification of the device and seek public comment. If FDA does not believe reclassification is warranted, no further action is taken, and the device remains Class III, requiring PMA. That's for a postamendment device.

Where appropriate, FDA will issue a final reclassification for the device. Existing devices may continue to be marketed subject to the general and any identified special controls if Class II, not exempt. Future devices of this type or changes to existing devices will be cleared for market via the 510(k) route.

Thank you.

DR. PAGE: Thank you very much, Ms. Shulman.

Does anybody on the Panel have any clarifying questions for Ms. Shulman regarding the classification?

(No response.)

DR. PAGE: Seeing none, we will proceed. And I'll now ask FDA for their presentation.

Ms. Wentz?

MS. WENTZ: All right. Good morning. My name is Catherine Wentz, and I will begin the presentation today regarding the classification and regulation of the membrane lung for long-term pulmonary support.

We are here today to discuss and seek the Panel's recommendation regarding the classification of the membrane lung for long-term pulmonary support. These devices are one of the remaining preamendment Class III medical devices. For Class III devices, premarket approval, or PMAs, are typically required for marketing. However, membrane lung devices for long-term pulmonary support are currently cleared and marketed through the 510(k) regulatory pathway, which is typically reserved for Class II devices.

The FDA team will present the available evidence that will be used to determine: (1) sufficient evidence of device safety and effectiveness; (2) the risks associated with the use of membrane lung devices for long-term pulmonary support; and (3) whether special controls can be established to mitigate the risks to health.

At the conclusion of this presentation, the Panel will be asked to weigh in on FDA's recommendation regarding the regulation of membrane lungs for long-term pulmonary support.

The FDA speakers today will be myself, Dr. Avila Tang, and Dr. Laschinger.

The outline for the FDA presentation will include a brief regulatory history of the membrane lung for long-term pulmonary support, a description of the devices cleared with long-term pulmonary support labeling, also referred to as ECMO, the indications for use, the reclassification efforts,

risks to health that the devices pose, the clinical evidence we have for these devices to date, which will include presentations by Drs. Avila Tang and Laschinger, and finally FDA's proposed regulatory strategy.

Here's a snapshot of the regulatory history for the membrane lung for long-term pulmonary support regulation. Membrane lung devices for long-term pulmonary support were originally classified by the Anesthesiology Device Classification Panel in 1982 as Class III devices.

The Panel's recommendation that membrane lung devices for long-term pulmonary support be classified as a Class III device was published as a final rule on July 16th, 1982 with the following codified language: "A membrane lung for long-term pulmonary support is a device used to provide to a patient extracorporeal blood oxygenation for longer than 24 hours."

Based on the original identification for this regulation, the regulation describes an oxygenator that would be used for long-term extracorporeal membrane oxygenation, or ECMO. However, ECMO is a treatment that utilizes an entire extracorporeal circuit and not just an oxygenator. Other devices included in an ECMO circuit would include tubing, heat exchangers, catheters, pumps, filters, et cetera. FDA has cleared through the 510(k) tubing, an oxygenator, heat exchangers, and catheters either under the membrane lung for long-term pulmonary support regulation or with ECMO or long-term use labeling.

This is a diagram depicting an extracorporeal ECMO circuit. As

you can see, the membrane lung is only one component of this circuit. ECMO cannot be performed with only an oxygenator.

So based on the fact that ECMO is only possible with a circuit of devices, our first proposed recommendation is to revise the regulation to include all the devices required for an ECMO circuit and to move the regulation from the Anesthesiology Panel to the Cardiovascular Panel since the circuit utilizes the same devices that are currently reviewed and regulated under the Cardiovascular Panel as cardiopulmonary bypass devices. The regulation name and identification revisions will be discussed in more detail later on in this presentation.

As I have indicated earlier, the FDA has cleared several extracorporeal circuit devices for long-term ECMO use or under the original membrane lung for long-term pulmonary support regulation. Specifically, tubing, an oxygenator, heat exchangers, and catheters.

Tubing was cleared in 1977 for use with roller pumps, which were the only pumps used for ECMO at the time. An oxygenator was cleared in 1986 for long-term ECMO, with labeling indicating use up to 32 days. The indications for heat exchangers and catheters clearly state that the devices are intended for use during ECMO procedures.

The 1995 515(i) order required the manufacturers of 27 Class III devices, including membrane lung devices for long-term pulmonary support, to submit to FDA a summary of all safety or effectiveness information

concerning the devices in order to determine whether the classification of the device should be revised or whether a regulation requiring the submission of premarket approval applications, or PMAs, for the device should be promulgated. Responses were required by February 14th, 1998, and on February 13th, a citizen's petition was received, providing information in support of reclassification of the membrane lung for long-term pulmonary support to Class II.

No final rule was issued for the 1995 order. So FDA issued the 2009 515(i) order for the remaining Class III preamendment devices. This order again required the manufacturers of the remaining Class III devices to submit a summary of adverse safety or effectiveness information concerning the devices.

Medtronic, being the only manufacturer of an oxygenator labeled for long-term use, was the only manufacturer to submit a response to the April 9th, 2009 order. The information consisted of a copy of the 1998 citizen's petition along with some minor updates and a new medical device report, or MDR analysis. Medtronic recommended that the oxygenators be reclassified into Class II based on the history of use for the device, the proposed special controls to mitigate the risks to health associated with the device, and the 30-plus-year data from the Extracorporeal Life Support Organization, or ELSO, registry, providing clinical information related to the use of ECMO for relevant indications or conditions.

Based on the feedback received from the 2009 515(i) order as well as our own knowledge base and understanding of ECMO, the FDA published a proposed order on January 8th, 2013, outlining our regulatory strategy for the membrane lung for long-term pulmonary support. In this proposed order, FDA proposed reclassification for the membrane lung for long-term pulmonary support from Class III to Class II. FDA further proposed to revise the title and identification of the regulation to reflect all device components used in an ECMO circuit, not just an oxygenator.

FDA believes that reclassification to Class II is possible when these devices are utilized to provide assisted extracorporeal circulation and physiologic gas exchange of a patient's blood when an acute reversible condition, that is, one that is not prone to recurrence, prevents the patient's own body from providing the physiologic gas exchange needed to sustain life in conditions where imminent death is threatened by cardiopulmonary failure in neonates and infants or where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery in all pediatric patients.

FDA received comments to the January 8th, 2013 proposed order from three sources. Once source agreed, and the other two had comments for FDA to consider. Details regarding these comments and the FDA responses were provided in the Executive Summary.

Regarding the two sources that provided comments for FDA to

consider, the main comments from Maquet were related to clarification in the scope of the patient population and clinical conditions being targeted for reclassification. The main comments from Public Citizen were related to control over design changes or new technology for a Class II device and also control over expanded clinical use for ECMO for new, unproven uses not called out for in the identification.

Based on the feedback received from the January 8th, 2013 proposed order and additional literature research performed on the patient populations in question, that is, the adult and pediatric patient population, FDA has added clarification to the original proposed identification to specify the following conditions in patient populations proposed for reclassification, specifically, acute respiratory failure in neonates and infants and cardiorespiratory failure or failure to wean in all pediatric patients.

The risks to health identified for the proposed extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support regulation are shown in bold above and were presented in the January 8th, 2013 proposed order. The first seven risks identified on this slide include the risks identified by the original Anesthesiology Panel in 1979, which are the first four risks in italics, and those identified in the 1998 citizen's petition, which are the three highlighted in yellow. One should note that these first seven risks were all based on the original regulation identifying an oxygenator only. The final four risks in bolded type have been added to

include the risks to health associated with an ECMO circuit.

The evidence used in our review to propose that extracorporeal circuit and accessories for long-term pulmonary/ cardiopulmonary support can be down-classified to Class II is based on safety and effectiveness information obtained from MDR reports, a review of the applicable literature, and clinical experience. This information is also used to identify the special controls necessary to mitigate the risks to health we just saw on the previous slides.

The FDA Executive Summary included a series of MDR reports, which attempted to tell the story of the difficulty in identifying adverse event reports related to ECMO procedures. In short, MDR reports are identified by device type. ECMO procedures require the use of an extracorporeal circuit, which can include many device types. So more often than not, it is difficult to determine which event may have been attributed to which device. Additionally, since most of the devices utilized in an ECMO circuit are being used off-label, it is difficult to determine whether the report was related to an ECMO procedure or a bypass procedure since most of the devices used in an ECMO circuit are also used for bypass.

Regardless, this table provides the most comprehensive attempt in identifying the issues related to an extracorporeal, as the search included nine circuit devices as well as the search term ECMO. The time period identified for the search was from January 2003 through June 2013.

The search yielded a total of 301 MDRs. Malfunctions were the most frequently reported type of event, with 48 reported deaths over the 10½ years.

Some of the device problems identified on these MDR reports include the need to replace the device; leaks; malfunction, with no other specifics; tear, rips, or holes in the device material; poor gas exchange; restricted flow; and increase in pressure. Blood loss was the only specific commonly reported patient issue.

At this time, I would like to present Dr. Erika Avila Tang, who will discuss the systematic literature review performed and the methods used.

DR. AVILA TANG: Good morning. I'm Dr. Erika Avila Tang, and I'll be presenting the results of a literature review on the use of extracorporeal membrane oxygenation that the Division of Epidemiology prepared for this Panel meeting on circulatory system devices.

I will briefly present the objective, methods, and findings of the literature review on ECMO use followed by a discussion of the strengths and limitations.

The first objective of this literature review was to provide safety and effectiveness information for the use of ECMO for cardiopulmonary and pulmonary failure in neonates and infants for imminent death in a potential reversible condition for the following four indications for

use: meconium aspiration syndrome; congenital diaphragmatic hernia; primary pulmonary hypertension of the neonate, idiopathic; and failure to wean from cardiopulmonary bypass.

The second objective was to provide any safety and effectiveness information for the use of ECMO for cardiopulmonary failure and failure to wean in adults. Dr. Laschinger will be covering the pediatric population, those between the age of 2 and 21 years old.

A search of the scientific literature was conducted using PubMed. The search was focused on publications on ECMO and its adverse events, contraindications, methods, mortality, rehabilitation, and statistics and numerical data, trends and utilization. In addition, the search was also narrowed to the indications for use previously stated, age groups of interest, human studies, and on articles published in English.

Articles were excluded from this review if they were case reports, small studies, or nonsystematic reviews. In additional, articles were not included if they didn't have results for ECMO, relevant age groups, or indications for use. Also, articles were not included if they were evaluating the use of ECMO in different settings or with adjunct treatments, or did not present safety or effectiveness endpoints related to the use of ECMO.

This slide presents the article retrieval and selection process for this literature review. There were 287 articles identified through PubMed and six from other sources. After removing duplicates, 277 abstracts were

reviewed and 190 of them excluded for the reasons listed on the previous slide. Therefore, 187 full-text articles were reviewed, with 25 being included in this literature review.

Out of the 25 articles identified, three presented data for more than one indication for use. Results for meconium aspiration syndrome and congenital diaphragmatic hernia were included in 6 and 13 studies respectively. Results for idiopathic PPHN, infant and adult failure to wean were each included in three different studies. The 25 articles were publications available since 1989, and there was a wide range in number of study subjects included.

Out of the 25 articles identified, the study designs included one meta-analysis, one randomized clinical trial, one before and after comparison of availability of ECMO, two cross-sectional, and 19 case series, which included a number of registry-based studies. The results of a clinical trial were published in two articles, but I present it here as one study. Seven studies were based on the Extracorporeal Life Support Organization international registry. And the others were conducted among patients in the United States, United Kingdom, Netherlands, France, and Taiwan. I will be presenting the results of this review by indication for use.

I would like to start presenting the results on ECMO use among infants with meconium aspiration syndrome. Out of the six studies identified, results from a randomized clinical trial were available. The U.K. Collaborative

ECMO trial randomized 69 infants with meconium aspiration syndrome to ECMO or conventional management. This figure presents the relative raise in 97% confidence interval for all of the babies in the trial and for those with meconium aspiration syndrome. As we can see, there was a significant reduction in mortality among babies treated with ECMO, with survival to discharge among ECMO patients of 81% and 57% for babies managed conventionally. This difference in survival was statistically significant.

Data on these patients were also available at four years, with more ECMO patients being alive or not severely disabled at four years compared to the patients treated on the conventional management. But this difference did not reach a statistical significance.

In this light, I present the results from the other status identified on the use of ECMO for meconium aspiration syndrome. One of them compares outcomes before and after ECMO availability. Survival among the 10 patients from the pre-ECMO period was 30% compared to 93% among the patients when ECMO was available. A similar survival was reported in another study among more than 3,000 patients with meconium aspiration syndrome from the ELSO registry in which there was more than 90% survival. Nearly two complications per patients were reported among another ELSO registry study, where the most complications were cardiovascular, mechanical, hematologic, renal, and neurological.

One of the articles identified for the use of ECMO among

infants with congenital diaphragmatic hernia is a meta-analysis which included two randomized clinical trials and a number of observational studies.

This figure presents the results of the two randomized clinical trials, which, in total, included 39 patients. As we can observe in the top figure, the results for the short-term mortality or survival before discharge favored ECMO, reflected by a relative risk below 1. Although the results for long-term mortality or survival after discharge were promising, this difference among the treatment was not statistically significant. In other words, survival before discharge among infants that received ECMO was 35% compared to a survival of 10.5% among those that received conventional mechanical ventilation. In the case of survival after discharge, 25% of patients supported with ECMO survived compared to only 5% among those with conventional mechanical ventilation.

This slide presents the results of the meta-analysis from the observational studies on the use of ECMO among infants with congenital diaphragmatic hernia. There were 19 observational studies with data for short-term mortality from 1,810 patients and eight studies for long-term survival from 774 patients. In this figure, we can observe that the results for both short and long-term mortality were similar, with infants receiving ECMO surviving 65% versus those not receiving ECMO surviving 44%. A study of more than 2,000 patients from the ELSO registry reported complications

related to hemofiltration, cardiac stunning, seizures, and cerebral infarction.

For idiopathic primary persistent pulmonary hypertension of the neonate, a study of 1,500 patients from the ELSO registry show among these patients a survival of more than 80%. The major causes of death were lack of lung recovery and organ failure. Among these patients with idiopathic PPHN, survival decreased the longer the patients were supported on ECMO, with only one-quarter of the neonates surviving at three weeks. On average, two complications per patient were reported. However, as we can observe in this figure, complications double if the patient was more than two weeks on ECMO support. The majority of the complications were cardiovascular and mechanical.

Three case series studies were identified for ECMO support due to failure to wean from cardiopulmonary bypass among neonates and infants. One of these studies was conducted among 39 patients weighing less than 3 kilograms. The one-month survival report among these patients was 67%. The two other studies were among infants with congenital heart disease, where survival at discharge was much lower, between 34 and 38%.

One of the three case series studies identified for ECMO use due to failure to wean from cardiopulmonary bypass among adults was conducted among 51 patients in Taiwan. The survival at discharge among these patients was 33%, and by one year 29% were still alive. Note the much lower survival among adults compared to the survival previously presented

for infants. The major cause of death was pulmonary infection, and complications reported included acute renal failure, femoral bleeding, and hematuria.

This literature review had a search strategy to ECMO and its related adverse events, contraindication, methods, mortality, rehabilitation, statistics and numerical data, trends, and utilization. In addition, the search was also narrowed to the indications for use, age groups of interest, human study, and to articles published in English. Although this approach is more efficient, as it increases the specificity of the studies to evaluate, the loss in sensitivity can result in lesser studies.

This literature review is strengthened by the fact that one randomized clinical trial and a meta-analysis of two randomized clinical trials with a large number of observational studies were identified for meconium aspiration syndrome and congenital diaphragmatic hernia. Furthermore, data from the ELSO registry were using a number of studies identified. Some of these studies include data for more than 3,000 patients.

I would like now to introduce Dr. Laschinger, who will discuss the clinical review of ECMO use.

Thank you.

DR. LASCHINGER: Hello. My name is John Laschinger. I'm a medical officer at FDA, and I'm a board certified cardiac surgeon, who also was fellowship trained in pediatric cardiac surgery and practiced as a

pediatric cardiac surgeon for a number of years. I'm also UNOS certified in heart and lung transplantation.

How do I move this? Unfortunately, I don't know how to operate the slide, though. It's not working. Oh. Sorry. It was on the next thing here.

Okay. The uses of extracorporeal membrane oxygenation, or ECMO, we are discussing today for the pediatric population are shown on this slide. For these patients, short-term support on ECMO is used to stabilize the patient during periods of severe respiratory failure or to allow recovery from myocardial stunning or cardiorespiratory failure that may follow surgery to correct congenital heart disease.

It should be noted that for successful ECMO use, early recovery of normal organ function must be anticipated. In general, ECMO therapy is not indicated where prolonged support is anticipated when severe underlying anatomic or pathological abnormalities of the heart or lungs will prevent recovery of adequate and native function or where the underlying etiology will make the patients susceptible to ongoing or repeated episodes of organ failure. For these patients, other modes of device therapy designed for long-term use, if available, should be initiated as soon as possible.

Although cardiorespiratory insufficiency in a newborn affects only 2% of all newborns, it's responsible for over 1/3 of all neonatal deaths. Regardless of the source, about 10% of all infants with respiratory

insufficiency, or 2 per 1,000 live births, will fail to complete the normal transition from fetal to neonatal circulations at the time of birth, resulting in primary pulmonary hypertension in a newborn, or PPHN.

The primary function of the circulatory system of both the fetus and the newborn is to deliver oxygen to metabolizing organs and return deoxygenated blood to the gas exchange organ, to replenish oxygen and to eliminate the waste product CO_2. In the fetus that's shown on the left, the gas exchange organ is the placenta, and its vascular connections are in parallel arrangement with other systemic organs remote from the pulmonary circulation.

In order to supply deoxygenated blood to the placenta and return oxygenated blood to the systemic organs, a series of extracardiac shunts, including ductus venosus, the ductus arteriosus, and intracardiac shunts, such as the foreman ovale are necessary. Elevated pulmonary vascular resistance is a normal and necessary state. With both, the function of gas exchanges transfer from placenta to the lungs and, therefore, from the systemic to the pulmonary circulation. The venous and arterial circulations are separated in series, and not only are the fetal shunts unnecessary, but their persistence may lead to circulatory compromise.

The transition from the fetal to a neonatal circulation thus includes: elimination of the placental circulation, lung expansion, a tenfold decrease in pulmonary vascular resistance, such that the increase in blood

flow necessary to accommodate the entire cardiac output through the lungs occurs, and closure of the foreman ovale ductus arteriosus and ductus venosus.

Failure of the normal cardiorespiratory transition at birth results in severe right to left shunting of blood through the fetal circulatory pathways and severe hypoxemia. Conventional treatment is aimed at lowering pulmonary vascular resistance through respiratory support and medical therapy. Avoidance of ECMO is always a goal.

A three-tiered classification of PPHN based on the underlying vascular and parenchymal abnormalities has been proposed and is a useful construct for our discussion of the available evidence for ECMO effectiveness in neonatal cardiorespiratory insufficiency secondary to PPHN.

The first is abnormally constricted pulmonary vasculature due to lung parenchymal disease such as would be seen in meconium aspiration and respiratory distress syndrome or in pneumonia. The second is where there is actual remodeling of the pulmonary vasculature with normal lung parenchyma, such as seen in idiopathic primary pulmonary hypertension, and is associated with certain drugs taken during the third trimester. And the third is hypoplastic vasculature, as would be seen in congenital diaphragmatic hernia.

The mainstay of therapy for all neonates with respiratory failure is mechanical ventilation, and the goals of therapy are to improve

oxygenation, achieve normal lung volumes, and avoid the adverse effects of high or low lung volumes on pulmonary vascular resistance. High frequency ventilation is commonly used.

Other treatments and their levels of evidence are summarized here. This table is reproduced in your packets for detailed inspection. It should be noted that following optimization of ventilation, inhaled nitric oxide has become evidence-based standard of care as has ECMO, though its use is reserved for continued respiratory failure despite optimal medical and ventilatory management.

Failure of medical and ventilator management is an indication for ECMO therapy. ECMO should be initiated prior to the onset of severely decreased oxygenation and acidosis. The most commonly used calculation in determining the need for ECMO initiation is the Oxygenation Index, calculated by the formula shown here. The threshold for initiation of ECMO is a calculated OI of 40 or greater.

A Cochrane analysis was performed to critically assess results of ECMO therapy primarily for primary pulmonary hypertension types I and II. A meta-analysis of four randomized clinical trials of ECMO versus conventional medical and ventilatory management was performed using data from Syracuse, Boston, Michigan, and the United Kingdom.

All children were age 0 to 28 days, with gestation greater than 34 weeks. The entry criteria included severe but potentially reversible

respiratory failure with a PaO_2 of less than 40 mmHg and a pH of less than 7.15 for greater than two hours and an Oxygenation Index of greater than or equal to 40. Outcomes measures were focused mainly on mortality and disability.

Conventional medical management during continued ventilation, as defined in the largest of these trials from the U.K., are summarized here and include liberal use of oxygen, correction of acidosis, maintenance of adequate blood pressure, paralysis, and use of any available pulmonary vasodilator, including nitric oxide, if the infant showed a poor response to the previous therapies. Arterial access for blood pressure monitoring was used uniformly, and high-frequency ventilation and surfactant were allowed.

Shown here is a forest plot of the risk ratios shown on the far right for death before discharge home for all eligible patients treated with ECMO versus those treated with ventilatory therapy alone. ECMO therapy was associated with a highly significant reduction in the risk of mortality, with the risk ratio of mortality for ECMO versus conventional medical therapy of 0.44.

When the 19 total infants with congenital diaphragmatic hernia were excluded, the results of ECMO therapy for primary pulmonary hypertension types I and II become more apparent. For these patients, ECMO therapy was again associated with a highly significant reduction in the

risk of mortality compared to conventional therapy. This risk ratio of 0.33 for ECMO versus conventional medical and ventilatory therapy represents a number needed to treat per life saved of 3. Looking at these same infants at one year of life, the survival benefit for ECMO versus conventional therapy was maintained and remained significant.

Finally, long-term follow-up of all eligible ECMO and medically treated patients in the U.K. trial showed that ECMO therapy was not associated with any significant increases in long-term death or disability. From their analysis, they concluded that the damaging effects of prolonged exposure to aggressive conventional therapy far outweighs the risk and damaging effects of ECMO. For patients without congenital diaphragmatic hernia, the approximate number needed to treat per life saved is equal to 3. Late mortality or disability is not increased by ECMO therapy for these children.

The policy of using ECMO in mature infants with severe but potentially reversible respiratory failure would result in significantly improved survival without any increased risk of severe disability among survivors. They also concluded that the overall effects of ECMO and congenital diaphragmatic hernia remain unclear.

However, ECMO is not without its problems. This slide shows the relationship between ECMO duration and complications per neonate on the left and the distribution of ECMO complications on the right for patients

undergoing ECMO therapy for primary pulmonary hypertension type I and II. As shown, the number of complications per neonate is increased as a function of ECMO duration. In addition to mechanical and metabolic complications, complications of almost every other organ system can occur during ECMO therapy.

This slide shows the result of the multivariate analysis comparing survivors and nonsurvivors with primary pulmonary hypertension receiving ECMO derived from a query of the ELSO registry for all neonates age 0 to 31 days of life with a diagnosis of primary pulmonary hypertension treated between January 2000 and December of 2010. This does not include children with congenital diaphragmatic hernia.

This analysis of 1500 patients reveals that, once initiated, the mortality risk of ECMO therapy is increased by prematurity and the profound acidosis and/or hypoxemia prior to initiation of ECMO. In addition, delayed initiation, greater than day of life five, or prolonged use of ECMO, greater than day seven, is associated with a higher risk of mortality. The association of significant physiologic derangement with poor survival should provide an impetus to initiate ECMO support before development of severe hypoxemia or acidosis in neonates with severe PPHN.

It was noted that nonsurvivors may have disease pathology distinct from PPHN, which include varying degrees of pulmonary dysplasia or hypoplasia, as it is associated with a delayed or insidious onset of

abnormalities that are more severe than those of survivors and remain irreversible despite ECMO stabilization.

Congenital diaphragmatic hernia requires a separate discussion due to its complex nature and lower survival rates for all therapies, including ECMO. With the advent of high-frequency ventilation and inhaled nitric oxide for PPHN types I and II, congenital diaphragmatic hernia, or PPHN type III, is now the primary indication for ECMO in neonates.

Congenital diaphragmatic hernia is a developmental defect of the diaphragm that allows abdominal viscera to herniate into the chest. The volume of herniated contents may be small or large enough to contain most of the gut, spleen, or liver because herniation occurs during a critical period of lung development when bronchial and pulmonary artery branching occurs. Lung compression by herniated bowel results in variable degrees of pulmonary hypoplasia. Approximately 80% occur on the left, as shown in this X-ray, and 15% occur on the right.

Congenital diaphragmatic hernia results in structural alterations of the lung, which are summarized on this slide. They include decreased number of pulmonary arteries per unit of lung volume, a decrease in the total arterial or cross-sectional area, significant adventitial and medial wall thickening in pulmonary arteries of all sizes and abnormal muscularization of the pre-acinar and intra-acinar arterioles.

Congenital diaphragmatic hernia occurs in about 1 out of every

2500 live births, and currently, there's no consensus on the treatment of babies with primary pulmonary hypertension. Prenatal tracheal occlusion is under investigation, and numerous modern ventilatory strategies have been tried, in addition to inhaled nitric oxide and ECMO. The restoration of abdominal contents of the abdomen is always required, and the optimal timing of surgery remains undetermined.

This defect is often associated with other cardiac, gastrointestinal, genitourinary, skeletal, or neural abnormalities, and trisomies. And these occur in up to 40% of infants. The association of these defects portends a poor survival. The severity of lung hypoplasia and the resulting degree of primary pulmonary hypertension is a primary determinant of overall survival in these children.

Despite subsequent introduction of advanced medical therapies, such as ECMO, inhaled nitric oxide, high-frequency ventilation, and surfactant, mortality for congenital diaphragmatic hernia remains substantially higher for neonates with congenital diaphragmatic hernia compared to other types of primary pulmonary hypertension types I and II and has not improved over the most recent decade.

The overall survival rate is reported as high as 80% in large specialized centers, where a greater number of children are born or transferred, as compared to smaller centers, where these cases are few and far between. Unfortunately, the wide disparity and the gravity of congenital

diaphragmatic hernia presentation prevents valid comparison of treatment results. Despite this, there is wide agreement that even if different types of ventilation, inhaled nitric oxide therapy, and ECMO cannot individually be proven to be truly beneficial to babies born with congenital diaphragmatic hernia, their conjunction or, at times, their alternance is beneficial and remains the standard of care.

In addition, when complete ascertainment of all cases is considered by taking into account the hidden mortality of either antenatal termination or postnatal death before transfer to referral centers, further uncertainty is introduced regarding the influence of these advanced therapies and improvements in outcomes for congenital heart disease.

The second major set of causes for ECMO therapy we're discussing today in the neonate and infant include the population where there is failure to wean from cardiopulmonary bypass, typically following surgery to repair congenital heart disease.

For postcardiotomy failure to wean, survival to hospital discharge has remained relatively static, approximately 40%. Poor survival for patients entered into the ELSO registry are predicted by support needed postcardiac surgery, for support initiated in the ICU, and for patients with single ventricle shunt-dependent physiologies. Both weaning and discharge was highest with patients with myocarditis and cardiomyopathy, and complications limit duration of support.

The size and extracorporeal configuration of the system components usually limit use to the ICU setting, making this a limited device as useful for bridge to transplantation since the patients must remain sedated, usually paralyzed, and there is limited opportunity for any rehabilitation while waiting for an organ.

For most of the causes of primary pulmonary hypertension types I and II, there is strong evidence, based on randomized controlled data, supporting ECMO use over standard mechanical medical therapy and ventilation for severe respiratory failure. Fortunately, newer modalities of ventilatory management and improved pharmacological therapy, including inhaled nitric oxide, have resulted in a lower need for ECMO therapy with similar mortality benefit.

For clinical situations where available medical therapy has failed and continued reversible cardiopulmonary failure exists, ECMO therapy remains the only viable options. For these patients with primary pulmonary hypertension, the survival benefit of ECMO has been clearly and repeatedly demonstrated and approached 80 to 90%. Given the absence of any other available therapy and an imminent outcome of death, equipoise does not exist for a trial of ECMO versus continued failed therapy in these patients.

Similarly, for more complex conditions and clinical presentations, such as congenital diaphragmatic hernia and postcardiotomy support, equipoise does not exist for a randomized trial since an alternative

to initiation of therapy for these patients after failure of medical therapy would also be death. For these patients, success of ECMO is a temporizing agent to gain respiratory and hematic stability and is highly dependent on rapid reversibility of the underlying cause.

With the clinical utility of ECMO for neonate and infant cardiopulmonary support in the arenas of reversible cardiorespiratory failure and failure to wean from cardiac surgery in the pediatric population clearly established and the benefit/risk profile for these uses generally well understood, FDA concludes that there is reasonable assurance of safety and effectiveness of ECMO circuit devices used in these patient populations.

Thank you. Catherine Wentz is now going to sum up.

MS. WENTZ: So I would like to finish up by summarizing some of the information we have just heard.

There appears to be sufficient safety and effectiveness data available to suggest that ECMO is the standard of care for reversible respiratory conditions for neonates and infants and in cardiorespiratory resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery in all pediatric patients.

Let's now turn to the identified risks to health and whether special controls can be established to mitigate these risks. The risks to health for the extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support are shown on this slide. As part of the

FDA questions to the Panel offered later in this presentation, you will be asked to provide your input on these risks to health and subsequent special controls for the extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support.

FDA believes that the risks to health can be sufficiently addressed with special controls, as identified in this list. For example, design characteristics, biocompatibility, sterility and shelf life will all be included as special controls and will be evaluated for each device.

Non-clinical performance evaluation will include comprehensive bench testing, including structural integrity testing, acute blood studies, electrical safety, electromagnetic compatibility, software, and reliability and durability over the intended duration of use. In vivo evaluation could include animal data and/or clinical data from prospective or retrospective sources to mitigate the long-term clinical risks, such as thrombosis and thromboembolism, gas embolism, hemolysis, and inadequate gas exchange.

And, finally, in addition to the required labeling information, a device with ECMO labeling will include information about the non-clinical and clinical evaluations performed and used to support the intended patient population and duration of use as well as specific device-related use, maintenance, and change-out procedures when used in an ECMO circuit.

It should be noted that additional detail was added to the

information provided here on this slide for non-clinical performance evaluation and in vivo evaluation of the device for clarity, as compared to the proposed order published on January 8th, 2013.

So, in summary, the evidence we have collected to support our proposal that the membrane lung for long-term pulmonary support can be reclassified from Class III to Class II in cases where imminent death is threatened by reversible respiratory failure in neonates and infants or failure to wean in all pediatric patients is based on the fact that ECMO is usually employed in the identified patient population after standard therapies have failed; the significant history of use of ECMO in the neonatal, infant and pediatric patient population and the extensive clinical data available; and the fact that the FDA has identified special controls to mitigate the risks to health associated with the use of ECMO in the identified populations and for the identified conditions.

Additional practical rationale for the FDA's proposal includes taking into consideration the unique circumstances surrounding the clinical practice of ECMO. For example, the current regulation is defined very narrowly in terms of both intended use, that is, gas exchange only, and technology, that is, a membrane oxygenator only. An ECMO circuit is comprised of individually manufactured and marketed components, and these components are put together by the practicing physician according to indication, patient population, and physician preference.

A broader definition and identification for this regulation, to include the circuit components and accessories needed for long-term extracorporeal support, will provide a regulatory pathway for all circuit components required for ECMO.

The revised regulation is written to include the flexibility needed to regulate future advances in technology through the 510(k) regulatory pathway. Indications or conditions where ECMO is not currently considered standard of care and are not identified in the reclassification proposal will most likely be considered a new intended use and would be subject to the PMA process or, if eligible, would be granted marketing authority through a de novo request.

And the special controls are written in a broader context to allow for some flexibility in the information necessary to mitigate the risks to health identified for the device. For example, FDA has proposed in vivo evaluation to demonstrate device performance. So depending upon the specific device characteristics as well as the available information, in vivo evaluation could include an animal study and/or clinical data, retrospective or prospective, to support the needed performance characteristics.

In summary, when there is an adequate knowledge base regarding the safety and effectiveness of the devices for the intended use and special controls can be established to adequately mitigate the risks to health, a Class II recommendation is appropriate.

As such, the FDA would like to recommend that the current regulation seen on this slide for the membrane lung for long-term pulmonary support be renamed, redefined, and reclassified as follows: The new regulation will be renamed Extracorporeal Circuit and Accessories for Long-Term Pulmonary/Cardiopulmonary Support.

The new identification will read as follows: "An extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support (> 6 hours) is a system of devices that provides assisted extracorporeal circulation and physiologic gas exchange of the patient's blood where an acute (reversible) condition prevents the patient's own body from providing the physiologic gas exchange needed to sustain life in conditions where imminent death is threatened by respiratory failure (for example, meconium aspiration, congenital diaphragmatic hernia, and pulmonary hypertension) in neonates and infants, or cardiorespiratory failure (resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery) in all pediatric patients. An acute reversible or treatable cause of respiratory or cardiorespiratory failure should be evident, and the subject should demonstrate unresponsiveness to maximum medical and/or ventilation therapy. The main components of the system include the console, the software and disposables, including, but not limited to, an oxygenator, a blood pump, heat exchanger, cannulae, tubing, filters, and other accessories."

And FDA proposes to reclassify the extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support as Class II with special controls.

Thank you very much. And this concludes the FDA presentation regarding the recommendation for the regulation for the membrane lung for long-term pulmonary support.

DR. PAGE: Thank you very much for that clear and concise presentation by the FDA.

I'll now ask the Panel if anyone has any clarifying questions. Again, this is not the time to discuss but to ask clarifying questions for the FDA.

Dr. Cigarroa, then Dr. Lange?

DR. CIGARROA: Good morning. This is Joaquin Cigarroa. Just like to ask two questions with regards to the literature sets and registries that were presented and/or data that was not presented.

Question number one would be why were studies and/or reports of the use of ECMO in the setting of adjunctive use of NO excluded if medical therapies today would include the use of vasodilators in this patient population, specifically in the pediatric population?

DR. LASCHINGER: I don't think they were. The U.K. study, in particular, which was part of the Cochrane analysis, did employ inhaled nitric oxide and surfactant, which is not vasodilator but inhaled nitric oxide is, as

part of their medical management. That made up 95 out of the 100 and -- I think there were 118 patients in the combined analysis, so it made up the vast majority of those patients. The other studies had variable medical therapy that might have or it might not have included inhaled nitric oxide. I think I showed that on my slide that inhaled nitric oxide was considered in those patients and certainly would be considered in any patient before ECMO therapy would be initiated.

DR. CIGARROA: Thank you. It was in the first presentation under exclusion of the 25 or so trials that were included in the literature search, which is why I asked the question.

DR. LASCHINGER: Oh, I'm sorry.

DR. CIGARROA: So thank you for those clarifying comments.

The second is under the objective number two with regards to adults with the postcardiotomy syndrome, in terms of the data presented. Any comments on inclusion or exclusion of the ECLS registry report that included approximately 2884 patients in their international registry and comments on that particular dataset?

DR. AVILA TANG: So particularly for the objective two on the failure to wean on adults, all the studies that were included was when it's specified that the failure to wean was -- or the ECMO was introduced or the patient had the ECMO support in their operatory room. So anything else that did not specify or specified that it was outside the operating room, they were

excluded.

DR. CIGARROA: Thank you.

DR. PAGE: Dr. Lange?

DR. LANGE: A couple clarifying questions.

Catherine, first of all, when you were talking about slide 21 -- the slide is not nearly as important as the comment that you made -- you said most of the use of the --

DR. PAGE: Could we pull up slide 21, please?

DR. LANGE: Right.

DR. PAGE: And I will mention that sometime during your presentation, you added a slide, so our Panel Packs have numbers that are one less than your slide definition. I didn't find -- I don't know where that was. It might have been in the 30s. But there will be a little bit of confusion in that our handouts have a different number. I think one slide was added sometime in preparation.

DR. LANGE: Catherine, when you talked about this slide, you made a comment that most of the use of ECMO this time was off-label. So at no time did we talk about what the current on-label use is.

MS. WENTZ: So say that again --

DR. LANGE: When you described this slide, you said most of the use of ECMO initially was off-label. So what is the current on-label use for ECMO?

MS. WENTZ: So there are only a few devices that have been cleared for ECMO use, and I had that up on a earlier slide, in 21. I think there was one oxygenator, a couple of catheters, a couple of heat exchangers. There are obviously several more devices in an ECMO circuit, so there is a lot of off-label use. Not only that, but a lot because of physician preference, they may not use the devices that have been cleared for ECMO. I know a lot of other oxygenators are being used besides the one oxygenator that was cleared for ECMO use. So it's very difficult to discern which of the devices that have been labeled for ECMO are actually in the MDR reports.

DR. LANGE: Thank you.

DR. PAGE: Thank you.

Dr. Jaquiss, then Dr. Balzer and Allen.

DR. JAQUISS: This is Dr. Jaquiss. I have questions about indications. There was a very nice review of both the neonatal respiratory failure population and then the failure to wean from a bypass in the pediatric population. But a very important usage currently is what's called the ECPR indication, which is a collapse in-hospital where conventional CPR has failed. The patients are then placed emergently on ECMO with presumably a recoverable circumstance. That was not addressed, I don't think, and that is an incredibly important usage in this day and age.

And then a completely unrelated question has to do with the fact that some of the devices that are now in use or are coming to market are

integrated devices with pumps and oxygenators. And you talked about cleared devices that have come through in alternative pathways. Because of a lot of the morbidity attended to ECMO is probably related to the pump in this day and age, how will that be dealt with in the regulation?

MS. WENTZ: So the regulation, as we're proposing, will include all of the devices needed in a circuit. And as I stated, it allows some flexibility for technology. The special controls and the performance testing, the bench testing, will be written so that the information that we need to see will be required of either a single oxygenator or a combination oxygenator-reservoir pump. We have some flexibility in our regulatory review to request the specific testing needed for any new technologies.

DR. LASCHINGER: Yeah. As far as the use of ECMO for resuscitation, it's not the intent of this regulation to inhibit the practice of medicine, and with an approved or a cleared device, excuse me, in any hospital, the uses for that kind of indication would be a practice of medicine decision that would be left to the physician.

DR. PAGE: Thank you.

Dr. Balzer?

DR. BALZER: This is Dr. Balzer. I just wanted to clarify a little bit on the definition or the inclusion criteria in the ECMO circuit itself because there are -- and I think you touched on this already, but newer devices like the PLAD, which is a pediatric lung assist device, such as Novalung, or

alternatively, things like ECMO circuits without oxygenators, where it's purely for cardiac support, my understanding is that they would be incorporated in this as well? Is that correct?

MS. WENTZ: So the cardiac support indications are not. The indications that we are discussing today are respiratory failure and cardiorespiratory failure for failure to wean. Cardiac support, we could not find enough information to support the safety and effectiveness for down-classification. So respiratory --

DR. BALZER: I'm sorry to interrupt. But in the definition here of what the ECMO components are, that would be included in that if you just -- regardless of what the actual indication is.

DR. ZUCKERMAN: Okay. We may be talking at cross-purposes, Dr. Balzer, which is why we need this clarification.

Perhaps if we put up slide 79, Catherine, and walk us all through it.

DR. PAGE: And, Dr. Balzer, can you turn off your microphone just while you're not speaking? Thanks.

MS. WENTZ: Is this the slide you're talking about --

DR. ZUCKERMAN: It's the problem that Dr. Page pointed out. I guess it's the next slide, where you have the recommendation where the full label is. There you go. What slide is that? Why don't you walk Dr. Balzer through that?

MS. WENTZ: All right. Well, really all I can do is read off exactly what the identification states. And I'll start there in the middle where imminent death is threatened by respiratory failure, for example, meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension in neonates and infants, or cardiorespiratory failure resulting in the ability to separate from cardiopulmonary bypass following cardiac surgery in all pediatric patients. And, again, the identification is very specific with the patient population that we feel we have enough safety and effectiveness data to reclassify to Class II. So the cardiac-only indications would probably be considered a new intended use and would require either a PMA or, if it qualifies, a de novo application.

DR. PAGE: Dr. Ohman, did you have a specific comment about that, because I've got other people in line.

Dr. Allen?

DR. ALLEN: I think we're still not quite clear, but maybe I can clarify that the -- what we're talking about now is an ECMO circuit that provides both oxygenation capability and gas exchange as well as circulatory support. What you were referring to, where you would provide just circulatory support would be analogous to a ventricular assist device therapy, and that comes under a separate guidance. Am I speaking correctly, Bram?

DR. ZUCKERMAN: Yes, you are.

And, Catherine, do you want to add to that?

MS. WENTZ: No, I was just about to say that's exactly right. So our VAD technology is regulated under a different regulation, and they are PMA devices.

DR. BALZER: Okay. Thank you very much. But then, to clarify, what about the PLAD type devices, like a Novalung, which is just an oxygenator, and the patient's heart functions as the circuit basically?

MS. WENTZ: Again, if the indications are analogous to what's up there, then that would fall under the reclassified ECMO.

DR. BALZER: I'm sorry to interrupt, but the point of clarification, it just says that -- the wording here just says, "provides assisted extracorporeal circulation and physiologic gas exchange." So if we're just talking about physiologic gas exchange with just an oxygenator alone, I just wanted to clarify whether this definition is indeed accurate that cover some of these other devices.

DR. LASCHINGER: Yes. What we're intending to cover here is the combined purpose of both cardiac and respiratory failure and not the single purpose of either cardiac, which would be a VAD, or just lung support. So those are separate indications that would remain under PMA at this point in time.

DR. PAGE: Dr. Laschinger, I've got to say, now I'm confused because as I read this packet, I thought the intent was to review gas exchange with or without circulatory support. And I think that's said in the

materials I read, but not circulatory support without gas exchange. So can we have clarification on that point from the FDA, please?

MS. WENTZ: Yes, I believe that's correct, that we're looking at the respiratory with or without cardiovascular support, but not the other way around.

DR. PAGE: Is that clear to the Panel now?

Dr. Balzer?

DR. BALZER: Not really. I'm still not certain. So if we had a device, the Novalung, for instance, that would be incorporated under this or it would not?

DR. PAGE: Could you define what that is, sir?

DR. BALZER: So Novalung is just basically a membrane oxygenator, where the patient's own heart functions as the pump. There is no roller pump or anything else in the in circuit.

MS. WENTZ: Understood. So if you are -- if the device is being used to correct a reversible respiratory condition, then it should be able to fall under this reclassification. The difference in technology is that you're not -- you're using a different circuit. As long as the indication remains within the bounds of what has been identified here, then that would be part of the reclassification.

DR. PAGE: I have a couple of other people who are in line, but Dr. Somberg, do you have a clarifying comment or question regarding this

specific topic? Okay.

Then, Dr. Balzer, are you clear and is the Panel clear now that -- my understanding again is we're here to review the situation where gas exchange needs to occur, and so we're replacing the lung with or without adding circulatory support. So gas exchange alone or gas exchange plus circulatory support, but not circulatory support alone?

MS. WENTZ: Correct.

DR. PAGE: Am I interpreting that correctly for the Panel?

MS. WENTZ: Yes, you are.

DR. PAGE: Great. Thank you very much.

Dr. Allen, did you have another question or --

DR. ALLEN: Yes, I do. I'm still confused about that so -- because I just want to make sure the FDA clearly -- because, essentially, what you're then saying is a bucket, for example, COPD support might fall into this category. I don't --

MS. WENTZ: No, COPD would not fall into this category. I'm not familiar with any infants that have had COPD.

DR. ALLEN: I understand that, but for -- so you're narrowing it down to the pediatric population, under 18, but the language in your things is -- it says one thing up there -- it's an "and" not an "and/or."

MS. WENTZ: Okay. Well, maybe that's something that we need to clarify.

DR. ALLEN: I think that's where the confusion is, is in -- because I have always assumed that it's combined, and I missed the language where it was a "and/or." I've only assumed it is combined, pulmonary/cardiopulmonary support.

DR. PAGE: So we will need to clarify that. And perhaps after the break, we can come back with improved wording.

DR. ALLEN: So I do have a question off of that topic, which is kind of the elephant in the room for me is how this affects applications of ECMO in adults and how that -- how this declassification may affect devices that are used in adults, and are those still going to then -- just so I clarify, need to know what level playing field I'm on when I'm discussing. And so in adults that might be on VV or AV ECMO with a cobbled together collection of devices off-label, all of that is still going to be Class III?

DR. PAGE: And before you answer that, if I could ask whether there is a regulatory definition for two words that were used in the presentations. One was adult and one was pediatric. And if there isn't, is that something that this Panel needs to address in terms of our recommendations?

MS. WENTZ: Okay. All very good questions --

DR. PAGE: Microphone, Dr. Allen, please?

MS. WENTZ: I'll start with the definition. The FDA definition of adult is anyone over age 21. Pediatric is 21 and under. So that's the FDA

definition. And for the purposes of our research here, that's what we used.

Regarding the use of a cobbled together circuit for adults, this reclassification is for the marketing of and the labeling for devices for ECMO. So the manufacturers, once this goes through, will be able to come in with 510(k)s and get their devices labeled for these specific indications. It's not going to change the practice of medicine. It's not going to change the way you use the devices if you feel you need it used that way. This just permits the manufacturers to have their devices labeled for this -- for the identification.

DR. ALLEN: So I guess just from a manufacturer's standpoint, I want to be very clear, because what happens sometimes is the nuances of labeling, as you well know, can be very important for companies. And so a company then can have their device cleared with a 510(k) for a pediatric labeled indication for ECMO, but they can't market it then for an adult application?

MS. WENTZ: That is correct.

DR. ALLEN: Okay. Thank you.

DR. PAGE: Dr. Zuckerman?

DR. ZUCKERMAN: Okay. But there's an additional caveat to that, Dr. Allen. Thank you for bringing up this very important point. We're at a time here where we have limited data per FDA review for the adult population. We would certainly encourage the industry to come in to talk

with FDA to rectify the situation, to do better adult trials, so that we don't have this distinction.

DR. PAGE: Thank you very much.

Dr. Cigarroa, I have three people in line ahead of you unless your comment is specifically regarding this issue.

DR. CIGARROA: It is specifically regarding this issue.

DR. PAGE: Please proceed.

DR. CIGARROA: I too have concerns about the implications with this reclassification as it relates to the adult population and would like again -- and the definitions are not provided under, at least what's accessible to me, under the ECLS registry report. But I'd like further classification as to the definitions of respiratory, cardiac, and ECPR, because that includes a population of almost 7,000 patients. And although the reclassification as it relates to the pediatric population does not impact our ability to practice within the adult, as we take a look at the implications, certainly in my state, and specifically for patients at risk as to what the state is willing to allow us to do, if there's not a marketing indication, then we are not able to provide certain services for certain patients.

So my question really is what is the issue with regards to the 7,000 patients reported that are adults in the ECLS that does not allow us to consider reclassification within the adult population?

MS. WENTZ: I'm going to let John, Dr. Laschinger, address that

in more detail. But from our research and the literature review that we performed, I'm assuming that the data that's out there was not, you know, collected in a controlled manner, and it wasn't data that we could use as valid scientific evidence to address safety and effectiveness.

DR. CIGARROA: What is the distinction between the data that we used in the pediatric population from the same registry report but precludes our using the adult data from that same registry report of over 100 centers internationally?

DR. LASCHINGER: Yeah. And I think the distinction is, obviously, we also looked at the registry reports in the children and neonates also. But the distinction was that we also had some randomized control trials from at least four different sources and a meta-analysis of those trials that also gave us as what we regard as high-quality clinical data.

Unfortunately, randomized clinical trials for adults for those same purposes, we didn't find enough support in the literature for that at this point in time. But, certainly, if those trials are done, we'd look at it very closely.

DR. PAGE: Thank you.

I've got Dr. Lange, Ohman, Somberg, and Yuh on deck, and Dr. Naftel.

DR. LANGE: And this is not part of discussion. It's actually for a clarification. And I share the same concerns that's been expressed. We're

basing this data upon the literature review that was provided to us. And the literature review seems to be limited. That is, it was limited, according to objective two, for adults, the IFU was failure to wean. And if you call up ECMO and cardiogenic shock, you'll pull up 409 articles. If you pull up ECMO and postcardiotomy, you'll pull up 109. I can pull up 15 studies now that report postcardiotomy use of ECMO in adults. And what we were presented with is one study. There were three that were identified. We talked about one, Hugh. And so my concern is that we're missing a huge number of patients. And yesterday, and I assume that today as well, is the scientific evidence wasn't limited to randomized controlled trials. It was limited to the wealth of all the data. And so between now and sometime in the near future before -- so I'd like to find out what the search terms were to make sure that we actually, basically, looked at the entire population.

It appears to me, so clarify this, is that when I look at how the searches were done, is that you identified already the four indications. And then based upon those four indications, one of which was failure to wean, then you did your literature search instead of doing it the other way around, where you say what's ECMO used for, what are the current indications and what are the data. So if you could clarify that and give me some assurance that we're looking at the data in totality.

DR. PAGE: And Dr. Laschinger, before you respond, I wonder whether at the break Dr. Lange could get together with you about the studies

that he specifically is noting to see whether those were caught in your literature review.

So let's put that on hold, Dr. Lange, if that's okay?

I will ask one other question --

DR. ZUCKERMAN: Well, let's take a step back, Dr. Page. The literature review was primarily done by our epi team, and they want to provide some clarity that will help our homework assignment during the break.

DR. PAGE: Perfect. Thank you. Yes, please, go ahead.

DR. AVILA TANG: Is this on? Yes? Okay.

So you want me to address it now?

DR. PAGE: To the degree you can, just in terms of your methodology, but I do think we need to get more granular in terms of the studies Dr. Lange is concerned about perhaps not being examined so that we have the data that are available to us as we're making this distinction between pediatric and adult indications.

DR. AVILA TANG: Sure.

So in the case as first looking into the ECMO, so these are the MeSH terms, which included specifics on ECMO, definitely that it was adverse effect, the contraindications and so on. Once that was put in PubMed, in the case of adults, in addition -- well, let me go back. For failure to wean -- that is the main question for adults -- the search terms included to be the

postcardiotomy and shock, or cardiosurgery and postoperative, or failure to wean, or failure to separate, or failure and wean or separate. So --

DR. LANGE: So, for example, if it didn't have the term postcardiotomy and shock, it wasn't caught? It wasn't postcardiotomy. It wasn't shock. You had to have both terms?

DR. AVILA TANG: Yes. However, potentially, some studies will have some of the other terms that were included.

DR. LANGE: Okay. And cardiomyopathy is not included in here? Myocarditis is not included in here?

DR. AVILA TANG: No.

DR. LANGE: Okay. Thanks.

DR. LASCHINGER: If I can make some comments? In my own personal search of the literature, I did obviously look at adult data and looked at failure extensively both from the ELSO registry and also from probably the largest single-center experiences in Germany, Dr. Mora's (ph.) group of 500 and some patients, and looked at that very carefully.

The data there is fairly inconsistent because it involves a whole host of different uses. It is not restricted to just several defined uses as we have in the pediatric population. It can be instituted both in the OR and in the ICU. It can be used for CPR. And, overall, the results are not as good. Instead of having an 80 to 90% survival, it's down to around 24 to 40% in various series, as high as -- I guess probably the highest single-center

experience I saw was around 65%. But that was with a limited number of patients. So that data may be skewed. But, overall, it seems to be up around 40% survival in the adult uses.

And the problem for the adult uses, there are -- as opposed to the children, there are other support devices that are available all along the way, including, you know, everything from, you know, balloon pumps to, you know, other devices that support the circulation both as temporary VADs and VADs that can be used along the way. And how those things sort out is much more complex than what we have for the pediatric population. So I think that's a more difficult problem for us to attack at this point. Certainly, it is something we're going to keep our eyes on in the future, as devices come on the market. But at this point in time, we're not as comfortable making the decision in adults as we are in children. I hope that clarifies things.

DR. LANGE: By the way, I think your summary is perfect. I think that's right on. But none of that data is presented to us. I mean, all we were presented with is one study from Hugh. And that analysis isn't available for us to evaluate. And so we're talking about reclassification of this for certain indications, and the question is should it be reclassified for that circumstance as well?

DR. LASCHINGER: Yeah.

DR. LANGE: So, John, I appreciate it. I think that's -- if that data -- if we could share that after the break, that would be terrific.

DR. LASCHINGER: Great.

DR. LANGE: Thank you. Very good.

DR. PAGE: Thank you.

While we're on the subject of the data available to us, yesterday, a number of studies outside the U.S. were rejected at the outset. However, in the Cochrane analysis, that's completely driven by an OUS study. Can you just help me understand why yesterday OUS was not acceptable and today, frankly, it's dominating our dataset?

MS. WENTZ: So I'll start here. So yesterday was cardiopulmonary resuscitation, external cardiac compressors, and CPR aids. And the procedures are, I think we discussed, are a little bit different in Europe than they are here, and that was the reasons why the OUS data was not considered heavily. But we also made the caveat that even if we had considered that data, it would not have altered our final decision anyway.

I think ECMO is a pretty standard procedure whether it's done here or in Europe, and I'll let John talk to that.

DR. LASCHINGER: And I think the major factor is that it was a randomized controlled trial and not a single-center experience or a registry-type data format. So I think the fact that it was a randomized controlled trial that was well done and well conducted by our analysis and by the Cochrane analysis, by their, you know, looking at the data and how the study was conducted. I think we have some certainty that data was collected in a way

that we would like it to be collected.

DR. PAGE: Fair enough. Thank you.

I'm going to ask Dr. Naftel to comment. He raised his hand, so it's going ahead of a couple of the other Panelists, but I think your comment was regarding some of the data that we've been discussing. Dr. Naftel?

DR. NAFTEL: Yes. So I don't want to get caught up in too many of the details, but there is one slide, slide 36, or maybe it's 37, or maybe it's 35 --

(Laughter.)

MS. WENTZ: Is that it?

DR. NAFTEL: That's it, right. So I just want to ask a few questions, because I know the Panel members and everybody, when you look at a slide like this, you have a choice. You can try to figure it out or you can believe it. So, you know, I guess I have a mission to try to figure it out.

So let's just look at it. So, you know, we're all friends here. So the first thing says -- in the white box says short-term mortality. So I say, oh, good, I'm going to learn about mortality. But then in parentheses, it says survival before discharge. And I say, oh. So when I look at those numbers under ECMO, 374 over 1084, I think those are the deaths. So it's not survival. This is mortality. So that's fine.

Okay. But then let's look at the B part. And I think -- I know you're dealing with the literature, but let's look at B, long-term mortality,

survival after discharge. Well, first of all, everybody is alive who's discharged, so 100% survival at discharge, but long-term, I just hate it when I see stuff like this, when it says long-term. You know, that's why God made Kaplan-Meier curves. You know, that's why we have that. I have no idea what we're comparing when they say long-term. What does that mean?

But let me even go a little further. So the conclusion, survival ECMO 65, no ECMO 44, well, in fact, if I take survival in the hospital for ECMO, it is about 65% based on these numbers. If I believe the long-term, then I'm looking at 406 who were discharged, and 144 died or the opposite lived, that's also about 65%. So the overall mortality is -- excuse me -- overall survival is .65 times .65. The overall survival is 42%. It's not 65; 65 is in-hospital. But if you're saying this is overall mortality, and that's what you're giving me, then it's actually 42% for ECMO. But doing the quick calculation of the no ECMO, it's 20%.

So something's really weird, because I don't actually believe that. I mean, aren't these babies -- this is all reversible stuff. Once they get out of the hospital, are they still subject to such incredible mortality? And maybe that's true, but -- so I've raised a lot of questions. And I know you're using the literature, but I think I don't know what survival is after ECMO, certainly not long-term, and if we could only define to being one year, two years, something like that. So I'm just a little confused.

DR. PAGE: Is this something you'd like some time during the

break to address, or are you able to answer it right now, Dr. Laschinger? Microphone?

DR. AVILA TANG: Okay. No, I understand your question, Dr. Naftel. The thing is, the majority of my presentation was related to survival, survival at discharge or survival after discharge, which many of the studies didn't -- did not provide what was the after discharge time.

So in the case of this meta-analysis specifically, because I wanted to present you with the specific figure and the data in more detail, they talk about mortality. And in that case, I'm presenting the short-term mortality and the long-term mortality as presented in the meta-analysis.

When I took it back to survival -- to be more -- and compare it to the other studies on the rest of the presentation, I calculated it separately. And as I mentioned in my script, it's more that the results for both short and long-term mortality were similar. I was talking, like, still is stratified. And -- because before discharge on ECMO was 65.5%, as you mentioned, and no ECMO, 46.8. After discharge on ECMO was 64.5%, and after discharge no ECMO, 42.4. So that's why I put it about 65% and about 44%. I didn't calculate it combined.

DR. NAFTEL: Yeah, so I think that's really important as we're looking at this. So 65% survival to discharge, great, and then once you're discharged, another 65% survival. So it's not as good as it sounds. It's actually quite bad.

DR. PAGE: Well, I think -- could you turn off your mike for one second, please? Let me see if I can clarify it, because this is confusing. A and B are different populations, I believe. So it's not that we lost 40% and then lost another 40%. If I'm interpreting this correctly, the meta-analysis for B only took patients for whom there was long-term, meaning they at least -- long-term defined as they left the hospital. So of those, you had a denominator of 406 for those studies. So the group A and the group B are different studies, if I'm interpreting your presentation correctly. So indeed it is 65% survival of all the patients who had ECMO placed in the hospital who were in studies that allowed follow-up beyond discharge.

DR. NAFTEL: I was with you till your last statement. So I think the correct statement is there's a 65% chance you'll leave the hospital. Once you leave the hospital, there's a 65% chance you'll be alive long-term?

DR. PAGE: No.

DR. ZUCKERMAN: Dr. Naftel, I don't think that's the case. I would recommend that during the break you personally work with Dr. Tang.

DR. LASCHINGER: I might be able to add some clarity also. For the trial with the longest follow-up was the U.K. randomized trial, and they followed patients out to seven years. And what they found of the 95 patients in the U.K. trial, 56 were still alive at seven years. Okay. So well over -- about 55% or so were alive total at seven years. And that was, you know, about -- I think it was between 80 or 90% left the hospital alive. So there is a falloff

after that in children due to other, you know, health problems, but not as a result, they thought, of actual ECMO therapy itself or a complication of ECMO.

DR. NAFTEL: So maybe I'm totally wrong. Maybe it really is in these long-term studies the denominator or the number of patients with ECMO, not the patients who were discharged alive.

DR. LASCHINGER: Um-hum.

DR. NAFTEL: If that's it, then I retract --

DR. LASCHINGER: I think that's the case.

DR. NAFTEL: -- all statements.

(Laughter.)

DR. PAGE: Thank you, Dr. Naftel --

DR. ZUCKERMAN: Do you agree with that last point just to close us?

DR. AVILA TANG: Yes.

DR. ZUCKERMAN: Yes.

DR. PAGE: Thank you. We have Dr. Ohman, Dr. Somberg, Dr. Yuh still on deck for comment or question. Again, these are clarifying questions for the FDA's presentation.

DR. OHMAN: Magnus Ohman here. I want to go back to your search terms again because the issue here is one of nomenclature in the sense that in the pediatric world, ECMO is used all the time, and then in the

adult population, it's cardiopulmonary support. You searched for one but not for the other. And so what we have here is that in the adult population, the key terms used for Medline searches are a little bit different. And I suspect that if we could see a search term for cardiopulmonary support, if that was what you have done, and then include cardiogenic shock in your search term, that I think will yield a different adult population that you might see. And maybe I'm wrong, but I suspect that that would be the case.

Maybe to clarify that for you, I know of at least three articles on cardiogenic shock where cardiopulmonary support was a search term and were published, and there were over 100 patients treated with cardiopulmonary support. And so it's not a trivial number, per se. And there's even a larger number, cardiac arrest, and I think that may be the challenge here.

DR. AVILA TANG: Yes. For that, maybe if we can make -- during the break, because even if they were captured, depending on their definition of failure to wean when the ECMO was implemented. So that -- and we can discuss also.

DR. OHMAN: Let me get back. There are other uses than failure to wean in this population. There's cardiac arrest. There's cardiogenic shock. There's a whole host of other things that happens in adults. And maybe this is not where we're going, but I just wanted to clarify that the search terms may have inadvertently led you down a path that you couldn't

find the articles that relate to the adult population in an easier way.

DR. ZUCKERMAN: Great comment, Dr. Ohman. And so there were two ways the literature in adults was looked at, through the formal techniques that our epidemiologists use, and then Dr. Laschinger did his own literature review.

Dr. Laschinger, do you also want to comment on that last point?

DR. LASCHINGER: Yeah. I mean, I did my own -- I'm not as a -- I don't have as formal a literature review apparatus as our colleagues do in OSB, but I did my own literature review looking at all the things that you looked at, and trying to go through all the various indications in adults as well as pediatrics, as I discussed previously. And I still stand by the same comments, that although, you know, there's a wealth of literature out there, mostly single-center experiences, it's kind of, you know, relates to devices that, you know, that are -- may or may not be used on-label or off-label and in various combinations. But the basic problem is, is that -- for all those things is that we don't really have any trials where it's formally compared to another therapy. So we don't know what the true results of that therapy is. As I said, most of the time, we see results in the 24 to 40% range for the most part, sometimes a little bit higher, sometimes, you know, a little bit lower. But, you know, how that compares to other therapies has really never been looked at in a systematic way, as far as I could find.

DR. PAGE: Thank you. Dr. Somberg, you've been tremendously patient.

DR. SOMBERG: Thank you for thinking -- John Somberg -- thank you for thinking that, but it's been a very good conversation, and I, too, am very concerned about the adult population and the use of ECMO. And I think while at least, Dr. Laschinger, you've made the statement that it may not rise to the level of the quality of the data in the pediatric population, over the last two days, we've had all sorts of different evidence quality.

So with that statement and my concern, I just wanted the FDA to think about and maybe address this at some later point, but the consideration is, at least from what I hear of this discussion, we're going to be down-classifying if we do vote in favor of it for the -- for a pediatric indication. And you'll then have really two -- a general area of the devices that have all sorts of potential permutations with or without an oxygenator, support and this and that, but you're going to be favoring the pediatric area and leaving a very vast adult area where it is going to be more arduous for industry.

So therefore -- and I wanted someone to address this -- I think you're going to be leaving the world with pediatric devices applied to adults as opposed to different types of devices and the different possibility of size exchanges and all sorts of things. So there may be an unintended consequence, and one should think these things out before one asks for what

one gets.

DR. PAGE: Thank you, Dr. Somberg.

Dr. Yuh and then Dr. Borer and then Dr. Lange?

DR. YUH: Yeah. I just wanted to make an attempt to clarify the curveball that Dr. Balzer threw at the Novalung device. I think that it wouldn't be included in this discussion, in this classification, because all of this discussion is really based on literature with a pump in line with an oxygenator. And so the putative predicate device, if you will, would be a mechanical pump in line with an oxygenator. I think they're different devices, because with an inline oxygenator with a pump, you have a fixed, you know, predictable cardiac output driven through the oxygenator whereas if you have a lung-only, an artificial membrane in line with a native heart, the cardiac output is variable.

So I think in an attempt to try to clarify that and what devices would or would not be included in this discussion, that that would not be one that would be included in this group of devices. I don't know if anybody wants to comment on that.

MS. WENTZ: Sure. Thank you. So as long as -- let's take an example. Say a device comes in and it is seeking labeling for the indication that we are discussing for reclassification, but it's also claiming that, hey, we can work without a pump, they would have to show that to us. And in one of the special controls, as I discussed, was in vivo evaluation, which would

include animal and/or clinical, either retrospective or prospective. So if we feel that the difference in technology is going to raise questions of safety and effectiveness that can be evaluated through clinical and/or animal data, then that's what we would ask for. But if the indication is the same as what we're discussing for reclassification, they can do that through the 510(k) process.

DR. PAGE: Thank you.

Dr. Borer?

DR. BORER: Yeah. I think you may just have answered my question, but I'm going to restate it anyway.

Two things. First of all, I may not be as sophisticated in doing computer searches as some are, and certainly not as sophisticated as the FDA epidemiologist, but it seems to me that if you use the same ECMO MeSH terms as infants and postcardiotomy -- I'm sorry -- and cardiac surgery and postoperative, you've got a pretty big net there. I'm not sure what you're going to miss that we're worried about having missed. That's one thing.

The second point, and perhaps I've misunderstood it, is that we're talking about the possibility of making it easier for certain devices that are developed to be used without going through a PMA. We're not saying that other devices, for example, even the same devices in adults can't be used. That would be regulating the practice of medicine. You can use them. You can test them. You can do whatever it is you were going to do, but if you want to get them approved for use, a new device, or an existing device for an

adult use, maybe we need more data than we have now, because it doesn't look as if the data are as clearly defined in adults as in children, as in infants. Have I missed that?

DR. PAGE: That's a very good point, but we'll save that for the discussion phase, specifically if you want to discuss changing the indication. What we're asking right now --

DR. BORER: No, I don't -- no, no --

DR. PAGE: -- is specifically about the data.

DR. BORER: But that is what I'm asking about. I'm asking about, you know, we've heard this presentation from the FDA, and I'm asking whether I am understanding correctly what the FDA is asking for.

DR. ZUCKERMAN: I think you've correctly perceived the correct spirit of the FDA's position.

DR. PAGE: Dr. Borer, are you satisfied?

DR. BORER: I'm very satisfied.

DR. PAGE: Great. Thank you.

Dr. Lange?

DR. LANGE: Just a clarification. If we could go to slides 31 and then slide 38, and it may be off by one. We'll see. I just want to make sure that -- because this will help frame our discussion. Thirty-one. So as I understand it, the studies that were used to form our recommendations are based upon these. And there are three studies that were looked at with

infant failure to wean and three with infant -- with adult failure to wean. And that's the totality of the data that we're talking about right now.

Can I go to slide 38 or 39? And the data with regard to infants that we're using are a case -- three case series? Is that right? No randomized controlled trials?

DR. AVILA TANG: Correct.

DR. LANGE: Okay. Thanks.

DR. PAGE: Fair enough. We have yet to hear from our Industry, our Consumer, and our Patient Representative. We will ask for your comments during the discussion phase. Do you have any specific questions to the FDA regarding their presentation?

Ms. Timberlake?

MS. TIMBERLAKE: Sharon Timberlake. I just want to know, as far as your MDR review analysis that was over a span of 10 years, did you see a decrease in the reporting for the deaths, and also for the device malfunctions, which was the number one reported?

MS. WENTZ: I actually didn't look at those trends, but we can pull that slide up, and we can take a look. I think it was pretty -- it's been pretty consistent. There are some years like last -- yesterday, we noticed that there was an uptick in malfunctions based on recall of a device. So, generally, I think they've been pretty consistent unless there's been a recall for a device.

MS. TIMBERLAKE: Thank you.

DR. PAGE: Unless there are any further clarifying questions from the Panel, I want to thank the FDA for a very nice presentation. And we have a little bit of homework to do at the break. We're way ahead of schedule. So to allow people to check out and to answer some of the questions that we've raised, why don't I suggest we reconvene still way ahead of schedule at 10:30.

Is that acceptable to you, Dr. Zuckerman?

DR. ZUCKERMAN: Yes. And before we break, why don't you try to again summarize the homework so we'll be able to clearly identify what's needed.

DR. PAGE: Thank you for the opportunity. And I'll let the Panel correct me if I'm not adequately capturing their concerns.

The presentation was very nice. There is concern that there may be more data out there with regard to adults. I'm hearing concern that the use of ECMO in adults is a standard of practice in some situations. And there's a desire, I believe, and we'll flesh this more out during the discussion, to possibly have us consider whether that should also be included as an indication. I'll need guidance from Dr. Zuckerman likewise as to what degree we can expand the suggested indications for this relabeling.

But what I would suggest is, specifically, Dr. Lange had some concern about some specific articles you just might want to make sure we

have the opportunity to examine as well as to see whether those were included in the original search.

Does that adequately describe the concerns, Dr. Allen?

DR. ALLEN: I think Dr. Naftel also had some statistical questions that he wanted to clarify.

DR. PAGE: Good point. We need to make sure that Dr. Naftel is satisfied with that slide and understands how the data are being put forward.

DR. NAFTEL: No. I was happy once I understood it wasn't survival after discharge; it's survival after implant. So I'm quite happy. Thank you.

DR. PAGE: Great. Thank you.

With that, we will reconvene at 10:30. I remind the Panel that no discussions should take place regarding the matter at hand other than specifically informational issues in terms of obtaining the data that we want to examine, and then we will report on that when we reconvene at 10:30.

Thank you.

(Off the record.)

(On the record.)

DR. PAGE: I'd like to reconvene. In terms of timing today, we are ahead of schedule. We're currently scheduled for lunch at noon and the open public comment section at 1, and we're obligated to be open for public

hearing at 1. If we do finish our deliberations before noon, we'll call lunch at that time and reconvene at quarter of 1. We have two speakers who will be speaking for up to 10 minutes each, and that way, we will be open for Open Public Hearing at 1 no matter what, in case there is someone who's scheduled to arrive at that time.

If we move very quickly, we could conceivably start the questions, but I think we're going to have plenty to talk about till at least 11:45.

So we're now opening up this section of our Panel meeting to Panel deliberations. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. In addition, we request that all persons who are asked to speak to identify themselves each time. This helps the transcriptionist identify the speakers.

At this time, I'd like to open the discussion to our Panelists.

Actually, before we do that, we had specific questions that were raised about the data. Do we have any update from FDA with regard to the questions in terms of the studies specifically that Dr. Lange mentioned?

MS. WENTZ: So this is Catherine. We did have some general discussions about the adult data, and I wanted to make the clarification, and I made the clarification in our small discussion here, that the 515(i) process is looking at the devices that have currently been cleared under this regulation.

And those devices that have been cleared for long-term use or under this regulation were basically for infants and neonates. And that's what our focus was on, although we knew that the adult indication was going to come into play. So we reviewed that data as well.

That said, we understand how the circuits are used, how the devices are used, the populations that they're used in. This is a good opportunity to get those devices and indications that are considered standard of care reclassified. So we will take the totality of the data back with us, and we will take another look.

DR. PAGE: Great. So that very nicely kind of summarizes our job today. During this deliberation phase, I want to be discussing the issues at hand, pediatric and adult, but again, our focus in on these cleared indications, which are as put forward by the FDA, and likewise, we will be addressing the questions as put forward. But we are advisory always, and this time, we're not even taking a vote. So I think it will be very valuable for us to convey the consensus as well as our individual opinions in terms of potentially other indications for ECMO. So is that fair?

With that, let's proceed with our open discussion. Who'd like to start things off?

Dr. Allen?

DR. ALLEN: Keith Allen. I certainly appreciate the FDA's flexibility in addressing the issue of adults, because I think that certainly

assuages my concerns about being transparent and not favoring pediatric versus adult for devices that are really actually used much more frequently in the adult world than they are in the pediatric world, at least in current practice.

I think what you're asking us to do seems very reasonable. Not too long ago we met with reclassification on different pumps, and this fits into that same category, where you're taking a technology that has a defined application and a defined patient population that has a reasonable wealth of data, perhaps not the scientific rigor that John might require, but certainly good scientific data, and a wealth of clinical use.

And with that in mind, I don't have any problems proceeding the way the FDA has outlined it, particularly when I'm assuaged that the adult population will get a second look.

DR. PAGE: Thank you.

Dr. Lange?

DR. LANGE: And, again, I appreciate the FDA's clarification as well. It's very helpful.

One of the things that I would either have -- elicit some discussion or have the FDA consider is in the current indication, it is for an acute reversible condition. And there are some conditions that may not be reversible but have a destination therapy, for example, a Berlin heart or a heart transplant, where the device could be used -- the condition may not be

reversible, the underlying condition may not be reversible, but it may be a treatable condition, and so to somehow incorporate that into the language of the recommendation.

DR. LASCHINGER: Yeah, I think when we're talking about reversible, we're talking about conditions where, when the device put in, there's an expectation that it could be reversible. In other words, you don't know whether somebody with myocarditis is going to recover their heart function or no, whereas something that's irreversible like COPD, it might be useful for that exacerbation, but does it change the person's long-term outcome is a different question than you might get. And, you know, so that's a whole different kind of --

DR. LANGE: And many of these conditions, we don't know, even with pulmonary hypertension, whether it's reversible or not. But there'll be some conditions that are not reversible, that is, an end-stage cardiomyopathy to an infant that is a bridge to a Berlin or a bridge to a transplant. ECMO could be used even though the condition itself is not reversible.

DR. PAGE: Thank you.

Ms. Currier?

MS. CURRIER: I have a question about the health of these children when they go home. When I was reading the summary, I gathered that, you know, it was fairly good. And then when I got to the appendix, I

found things like respiratory outcomes, chronic lung disease, 56%. And I went, yikes, you know, this is kind of bad. Cerebral palsy, 6%. So this is not, to me, a real successful outcome.

DR. LASCHINGER: Well, it --

MS. CURRIER: I mean, is the only success --

DR. LASCHINGER: I mean, compared to the alternative.

MS. CURRIER: -- is just lack of death?

DR. LASCHINGER: Yes. I mean, basically, the other alternative is death and doing nothing. And so from that perspective, I think it is a good outcome. When you look at the long-term U.K. data for death and disability both, it still favors ECMO at seven years. So children who are treated with ECMO are still doing better as far as disability goes at seven years compared to just standard medical therapy children that survive.

So the ECMO itself doesn't cause the long-term disability. It tends to be more the constellation of other things that are wrong with the children that occur in the children as well, along with the hypoxic insult they have prior to initiation and things like that.

So, you know, I think, you know, most people, you know, would take from the data that, you know, it's better to initiate ECMO sooner rather than later and things like that to avoid those problems. But it's not a consequence of the ECMO therapy that the long-term disability occurs for the most part.

MS. CURRIER: Yeah, well, I --

DR. LASCHINGER: There are strokes and things that occur on ECMO, obviously, and intracranial hemorrhages and things like that. But when you balance against medical therapy, it's not a higher incidence of those kinds of problems.

MS. CURRIER: But it's leading up to ECMO that could cause brain damage, too, right?

DR. LASCHINGER: Partially, yes.

MS. CURRIER: Yeah.

DR. LASCHINGER: And that's not to say that there's no brain complications of ECMO. I'm not trying to imply that. But a lot of it is determined by other problems that children have.

DR. PAGE: Thank you.

MS. CURRIER: Thank you.

DR. PAGE: I'm going to call on Dr. Cigarroa in a moment, but I just want to give a heads up to Dr. Balzer, Dr. Jaquiss, and Dr. Reich, being our local pediatric experts, I will be asking for you to comment in a few minutes as well during this discussion period.

Dr. Cigarroa?

DR. CIGARROA: Just want to come back to the issue immediately prior to the break and during the break and then the summary statement afterwards with regards to adults that I'd like some additional

clarification. We stated that we were going to focus on approved indications. And I just want to go back to slides 2 and slide 16. And I wonder whether or not as a result of the extensive discussions that we've had with regards to adults, whether the objective listed should focus primarily in the pediatric population or not based on the discussions we've had and, therefore, that slide 2 and slide 16 should then be amended to reflect that or not?

DR. PAGE: Can you clarify what you mean there, Dr. Cigarroa? I'm sorry.

DR. CIGARROA: Sorry for the confusion. The issue with regards to the data that we have looked at and the desire to reclassify from Class III to Class II is primarily, I believe, indicated today with regards to the categories of the pediatric population. Given the issues that were discussed before the break, during the break, and summarized immediately afterwards, I wonder whether the -- those slides need to be amended to reflect that.

DR. PAGE: Again, I think these slides accurately reflect what the FDA came in with, and as such, they should stand as they are. You bring up the very important point that has been discussed, and that is, what about adults. And what I'm going to look for us to do in terms -- not necessarily in terms of the open discussion period, but when we go through the questions is make sure we address the questions at hand, because Ms. Wentz has just educated us in the reason for which we're specifically looking at the pediatric indication. But you and others have brought up the very important issue of

adults, and we want to make sure that we give advice to the FDA with regard to future indication and labeling for ECMO in the adult population.

Is that acceptable to you, Dr. Cigarroa?

DR. CIGARROA: I believe so. I remained concerned that the broad terms used are unintentionally misleading and would have unintended consequences. That might be addressed as you stated, and we'll see.

DR. PAGE: Fair enough.

DR. CIGARROA: Thank you, sir.

DR. PAGE: Thank you.

MS. WENTZ: If I could add some clarification, is that possible?

DR. PAGE: Yes, please.

MS. WENTZ: Just regarding the process, our process, which is not always as transparent or as clear to you all as it is to us, so we will take all of the comments from this Panel meeting back with us and can make revisions for our final order. What is stated here is the information that we had, and we received to the proposed order, and the recommendation that we put forth today does not necessarily have to reflect the final order that will be going out. We need to consider all comments.

DR. PAGE: Yes, Dr. Cigarroa?

DR. CIGARROA: Thank you. That helps.

DR. PAGE: Dr. Jaquiss?

DR. JAQUISS: At the risk of flogging the horse that seems to be

dead -- this is Dr. Jaquiss -- I think it is worth considering when we're talking about the evidence and looking again at slide 2 that was just referred to, do we have sufficient evidence of safety and effectiveness, it's worth recalling the history of this ECMO, which, obviously, everybody understands, I think, is an incredibly complex technology, but it was developed as a respiratory support apparatus which happened to have a pump with it because nobody could figure out any other way to get the blood to flow past the lung. And over time, that's altered. And so in different populations, its effectiveness has been applied for different physiologic derangements.

But the difficulty in the evaluating the evidence is that the studies that were very nicely summarized in pediatrics where there was a randomized controlled trial, for example, of ECMO as a respiratory rescue, and where the results are really very good, neonatal pulmonary failure, whether it's from persistent hypertension of the newborn or meconium aspiration, or group B strep sepsis, et cetera, there you can compare it to best medical therapy, which is a ventilator with some tweaks of pressures and oxygen concentration and so forth.

When we're talking about it as a cardiopulmonary support, there is no best medical therapy. If we're talking about failure to wean, the alternative, the randomized prospective trial if using ECMO versus failure to wean from bypass is turning the bypass pump off in the operating room and saying you're dead.

In the case of extended CPR, which is a very common indication now in children's hospitals -- I had this conversation recently with an emergency room doctor who wasn't willing to have this technology used in his emergency room because there were no randomized prospective trials. And I asked him to contemplate how that would be constructed. So in one arm, you would have a child who was getting CPR that wasn't working who was going to die and put him on ECMO, and in the other arm, you'd let him die.

And so you can't really hold the adult data, which is much more likely cardiopulmonary support than pure pulmonary support, to the same sort of level of evidence that you might have held the neonatal respiratory stuff to. So I take John's point, Dr. Laschinger's point, about how the level of evidence is not what it might be in the neonatal population, but it's unrealistic to expect that it ever will be. And along the lines of is it successful, it's successful if you have a live patient at the end of it, because the alternative is certain death.

DR. PAGE: Thank you very much.

Other comments? I put Dr. Balzer and Dr. Reich on notice. I do want to hear your perspectives, but Dr. Ohman has a comment.

DR. OHMAN: Yeah. Dr. Ohman here. I'll let them have a little bit more time. I just wanted to reemphasize what I said in the prior sort of clarification section of our discussions, that I think there is a lot more

literature in the adult population that we can sample from and better understand it. And by doing so, I think, not within the construct of today, but in due course, to actually get a clearer picture to exactly what Dr. Jaquiss talks about, namely, what is the current use in the adult population, is it temporary or is it bridge to another aspect of care, is it reversible or not reversible? Many things in the adult population are not reversible, but they have a bridge to something else. So I think there's lots of opportunities here for the Agency to sort of gather that information, maybe using different search terms, as I pointed out, and then gather that information, recognizing that the -- there will be no randomized trial, to my knowledge, or it could be some small ones that I have missed, but the reality is that there is a current usage with a established evidence of safety and performance that could be evaluated to look at in the adult population.

DR. ZUCKERMAN: And, Dr. Ohman, what are the top three adult uses that you could see in that sort of literature review?

DR. OHMAN: Well, I'd be interested in the other Panel members' comments on this, but cardiac arrest is one, refractory cardiogenic shock in the young, where the underlying condition is potentially something that would allow you to go on to other support devices. The pulmonary emboli is one that I have seen this used in. And I'd be fearful that I will -- at the spot of the moment, Dr. Zuckerman, I can't come up with all the indications, but refractory cardiogenic shock falls into that realm. So those

are the --

DR. SOMBERG: (Off microphone) bridge to transplant?

DR. OHMAN: Well, bridge to transplant, as Dr. Somberg points out, is a bridge to something, and so that's -- those are the larger indications that I can see.

DR. ZUCKERMAN: Okay. And if other people could comment in that broader perspective, it would be helpful, because as Dr. Jaquiss pointed out, there are a whole gamut of buckets certainly in the adult population. I think I heard you say one would be bridge to a more definitive circulatory decision, because, you know, for use in ARDS, I think there are randomized trials that have shown negative results. And so if you can help and others provide that granularity, that would be most welcome.

DR. PAGE: Dr. Allen?

DR. ALLEN: That's a very good question. And I think the key failure on the search is to have tied everything to failure to wean. So, actually, ECMO following cardiopulmonary bypass at most institutions isn't used. You don't need the pulmonary circuit when you fail to wean off bypass. What you typically have is pump failure, and you need a pump. So you use standard ventricular support devices. So at least in our hospital, and I think in most hospitals, ECMO isn't usually utilized outside of a congenital pediatric population and an adult population.

But there's a whole range of ECMO. I've got a patient in my

unit now that I put on ECMO for H1N1 who also had cardiomyopathy, and it's associated with respiratory failure. I got a patient in my unit on ECMO who came in in cardiogenic shock, 26-year-old female with myocarditis, who also has, you know, forward pulmonary edema. We couldn't support her. And she needed to be on AV ECMO. But you couldn't decide whether she was going to be -- recover, and the devices for, for example, VAD support are so expensive now, most people don't support people with bridge to decision with expensive ventricular assist devices. They'll simply put them on ECMO because it's quick, very expeditious, and it's relatively inexpensive.

So I think you have to look at other categories besides failure to wean because that actually is a very low group of patients -- somebody that presents in the ER with acute myocardial infarction and needs not only ventricular but pulmonary support. And then you have a whole separate bucket of patients that need VV ECMO or veno-veno ECMO, where all you're really doing is supporting their pulmonary circuit. They've got a good heart, but, for example, somebody that has a respiratory virus, H1N1, comes in in respiratory distress. They don't have myocardial involvement, but they just need to be supported with ECMO that purely involves the respiratory circuit. And that's actually probably a much larger market or a larger bucket than AV ECMO, at least in our hospital.

DR. PAGE: Thank you.

Dr. Jaquiss?

DR. JAQUISS: Just adding indications, certainly, in a center that does lung transplantation, venovenous ECMO is absolutely mandatory to salvage primary graft dysfunction that is a reversible indication. It's now increasingly used, ambulatory venovenous ECMO in our center for, particularly, adolescents and young adults who have cystic fibrosis and are awaiting lung transplant. We get them off the ventilator, put a venovenous cannula in them, and they walk around, and except for having a big cannula sticking out of their neck, they look like civilians. And that's been a terrific usage.

And I am not an adult practitioner, obviously, or I confess that freely, but there is a trial of VV ECMO, the CESAR trial, in the United Kingdom, which was, I think, a very high-quality study which was very suggestive, I think, of the utility of VV ECMO, the efficacy of VV ECMO, versus best medical therapy, or at least being cared for in an ECMO center with that bailout. And perhaps one of my adult colleagues could comment on that more intelligently, but that's a very well-known trial, and I think has motivated a lot of centers to think about VV ECMO much earlier.

DR. PAGE: Yeah, anybody familiar with that specific trial?

Dr. Allen?

DR. ALLEN: Dr. Allen. Yeah, the CESAR trial is a very interesting trial. I think before you throw that out as the end-all, be-all study, there are a lot of criticisms of that trial in that one of the criticisms of VV ECMO, to be

very transparent, is that a lot of centers jump to that, and there's been a lot of innovations in ventilator care, using different types of inhalation agents, different positioning, in order to get better results. And one of the criticisms of the CESAR trial was, too, either they delayed transport to a program that could do ECMO, which biased the results, or they didn't use -- they didn't all stick to state of the art ventilatory support recommendations.

DR. PAGE: Okay. Thank you.

Dr. Reich, did you want to make a comment, and then Dr. Borer?

DR. REICH: This is Dr. Reich. So the slide says -- speaking as a pediatrician, the slide says, "Do we have sufficient evidence of safety and effectiveness," and I would say the answer is yes. I think, clearly, in pediatrics, we have sufficient evidence. Then the second question says, "Can special controls be established to mitigate the risks?" I think there's two factors. One is what Dr. Jaquiss said, that there's indication creep, and that we use it for more and more indications. And it may be that some of the indications, it doesn't work as well. And the second answer would be it depends on what comes in. If you're getting reports of bleeding, then we may need special controls for bleeding. It depends on what side effects we're seeing. And maybe at some point we'll see more of one side effect than another and have to change the controls. But that would be my opinion as a pediatrician.

DR. PAGE: Fair enough. Thank you.

Dr. Borer?

DR. BORER: Yeah. I don't do surgery. I only go near patients with knives at dinner. That's the only way I'm allowed to do it, but you know, in the areas in which I focus, which are valve disease and heart failure and, to a lesser extent, chronic stable coronary disease, we just don't use ECMO in the adult. It's not that it couldn't be. It's not that it shouldn't be. But ventilatory support generally is sufficient to get people past the acute urgencies they have.

And now, you know, what I've heard here are multiple situations in which ECMO might be used and could be used and maybe should be used. I would say that this is probably beyond the scope of what we should be talking about here since the FDA has already said they're going to go back and take another look. If the data turn out to be much more extensive than what we've heard about and compelling, well, then the FDA can ask a question if it wants to of an advisory panel. But I don't think we should be spending a great deal of time in getting into the adult area at this moment.

DR. PAGE: I think you raise a good point. And I want to make sure we have a full discussion of the question at hand. That being said, this is a good opportunity for this expert Panel to -- thank you -- this expert Panel to give its opinion regarding this other indication. And the FDA has actually

welcomed that.

But what I might suggest is for the next 15 minutes or so, we focus on the proposal that was put forward to us. Any comments or concerns about the questions put forward? Safety and effectiveness? We'll go through these in the question forum as well, but in terms of safety, effectiveness, identified risks and special controls, and perhaps more broadly, relative comfort with what could be called down-classifying or reclassifying from Class III with 510(k) to a Class II with 510(k) possibility.

Dr. Yuh?

DR. YUH: I just wanted to get some -- a better sense from FDA about the consequences of reclassifying this from a Class III to Class II device in terms of postmarket surveillance. Is it true that minor manufacturing changes can be made on an approved device without notifying FDA, or is that a -- is that not true?

MS. WENTZ: So under the 510(k) paradigm, they can make minor manufacturing changes without coming into FDA, yes.

DR. YUH: And the only reason I ask that is that these devices are so critically important in that mechanical failure can result in catastrophic consequences, that how do you determine what is acceptable in terms of a manufacturing change that doesn't need to be reported?

For example, we had a stent element in our unit where it wasn't a design flaw, but rather, there was just a malfunction of an

oxygenator casing whereby the patient basically exsanguinated, and there was no way that anybody with even the most experience could have recovered from that. Again, it wasn't a design flaw. It wasn't a manufacturing defect, per se, a material defect, but nevertheless, the company did make some kind of an arbitrary change in how we handled the oxygenator to try to preclude any further incidence.

I mean, how do you know -- from the FDA -- what is acceptable and what needs to be reported and what doesn't in terms of minor changes, because even a minor change can result in a catastrophic failure of these devices?

MS. WENTZ: Correct. So obviously, we don't have control over all the changes and what the possible consequences are going to be, and there are going to be surprises, such as what you just described. No one would have ever, you know, considered the consequence of that minor change. The FDA does have guidelines out there for industry that permits industry to determine whether or not the change that they are making to the device is a significant change, it needs to come in with a 510(k), or is not a significant and they can just, you know, record the change and put that in their files.

That said, we do have inspections, and our inspectors go in and look through the files, and they are in contact with us. And they say, you know, they let us know what changes were made to make sure that the

decision made by industry is the correct decision. For the most part, as a reviewer, the industry is pretty conservative. And they make changes, and they're going to come, because they don't want to be caught red-handed or caught in a situation like you just described.

DR. ZUCKERMAN: Okay. But Dr. Yuh, you know, certainly, you've heard that we would propose to very carefully regulate this class of devices through the Class II pathway and utilize our 510(k) change and modification guidance document. But there's an additional component, actually, that I'd like you and others to think about and give us some advice.

You know, right now, we have a system where there's widespread off-label use of these devices, and that's why the Agency has proposed what we think is a rational way, where the industry and clinicians will work with a regulatory agency so that, going out the door, we will hopefully have a higher comfort and safety level with certain systems.

But even the best-laid plans have problems, and I don't mean to put you on the spot, but you and others have been here the last two days. You understand the problems with MDR underreporting. You may or may not want to comment on whether a separate MDR was sent to the Agency for this particular problem. There is the ongoing ELSO registry which the Agency plans on utilizing heavily. And certainly we want to work with the stakeholder to make sure that it can supply us appropriate information. But the real question is how do we improve the communication from the real

world use to the FDA?

So I'd like to throw the question back to you. And Dr. Ohman is smiling, and maybe he can help the FDA also.

DR. YUH: That's a great question. And I've always been somewhat puzzled, and I haven't really gotten a satisfactory answer as to why there hasn't been development of a more sophisticated adverse event reporting mechanism. It just seems glaringly inadequate. There's no denominator, in most cases, so how do you know, even if a large, you know, relatively large number is really significant or not on a widely used device.

So I guess, you know, the general question I have is there must -- with all the regulation, the oversight and the consequence of failure so significant, why there isn't a more sophisticated, going forward, mechanism for reporting, you know, at least catastrophic failures. Not necessarily relatively minor misadventures, but you know, things that have consequence, morbidity, mortality, to patients that can be directly attributed to the device. And I know it's probably easier said than done, but the MDR, it just -- it seems like -- it's frustrating to the look at the data each and every time we go through this because I don't know what to derive from it.

DR. PAGE: Before FDA responds to your question, I think we, as a medical establishment, need to take some responsibility ourselves. I just last week saw a clinical vignette at a regional meeting, where an unusual drug reaction was reported as part of the clinical vignette by a resident. And they

went through the literature, and there were six reported cases of this interaction. And it sounded very infrequent. And I asked the resident, well, did you report your case? And, of course, it hadn't been reported. So both the numerator and the denominator are inadequate. And the numerator part actually comes down to us physicians. I won't ask for a show of hands as to who's ever gone into the MAUDE reporting system. Personally, I have. And it's not as hard as it seems, but it is a little bit of extra work in a busy day, when sometimes you're taking care of a sick patient.

So I welcome FDA's response, but I felt I should at least acknowledge that our profession can do better as well.

MS. WENTZ: I absolutely agree with Dr. Yuh, and I think a lot of people at FDA agree as well. The MDR database is a voluntary database, so we are at the mercy of the reports that are being submitted.

That said, we are constantly surveilling the MDR reports, and we do have mechanisms by which we can flag when we feel the reports have reached a certain level that we need to start taking a look and possibly taking action. So that is constantly being done, albeit the numerator may not be as accurate as we'd like. But, again, it's a voluntary system.

DR. PAGE: Thank you.

Dr. Ohman?

DR. OHMAN: Thank you, Dr. Zuckerman, for catching me smiling. I have to say that this is a very challenging area, because as Dr. Page

pointed out, it is our, I believe, moral responsibility to report this to the larger community, including the FDA, but we fall down many times in this particular issue. My particular solution to this, which I actually want to congratulate the Agency for doing, I think there are devices where, particularly high risk, where registry information, collecting consecutive patients by a regulatory demand to do so is actually the right way to go.

I recognize that there are many people who do not believe that this is helpful, but I do believe it adds this level of security and understanding for rare events until the technology become mature. And when it becomes mature, as we have discussed the last two days, downgrading the classification to a level two is actually very reasonable because we have a lot of experience, notwithstanding that with any technology, things can go wrong. And don't think that we can capture everything that can go wrong, but I do believe for certain high-risk devices, a consecutive patient series from all sides in the country using this device that is high-risk offers us as practitioners and knowledge base to help us understand rare and unintended consequences of rare events that we simply don't know about.

I don't know if, Dr. Zuckerman, that is helpful.

DR. LASCHINGER: Yeah, I think it's very helpful. I think registries are definitely useful. I think as a clinician now speaking, not as a regulator, I have to say that in 20 years of what I would consider a fairly busy practice, I had never heard of the MDR database, so I didn't know it was

something you could report into. And yet, when you look through these registries, I recognize every one of the complications reported in there, and that's something I might have seen from somebody else's patients, of course, but in my hospital.

And so it's, you know, I think the registries are very useful. I think they offer us certainly a more granular snapshot of what's happening in the real world and what we're getting now through a voluntary, poorly understood reporting system. At least from the clinician's point of view, I think it's poorly understood.

DR. PAGE: I've seen the hands of Dr. Slotwiner, Borer, Somberg, and Jaquiss. I'll ask in that order if your comment is specifically on this topic to speak up. And, otherwise, you'll have your turn in a moment.

Dr. Slotwiner?

DR. SLOTWINER: Thank you. Back in 2006, when we were having problems with a particular defibrillator lead, we joined MedSun and HeartNet at the FDA. And so we've been -- we've got a system in place in our hospital where if there's any problem with any device or a suspected problem, it's very easy to submit a report. And I'm curious where that fits in with the MAUDE database and why or if that's something that the Agency could promote. Once that's set up at an institution, it makes it very simple to easily report these.

DR. PAGE: Thank you.

Dr. Borer?

DR. BORER: Yeah. I think Dr. Ohman's point about consecutive patient registries is right on target, and the FDA knows that. I mean, they do that.

The issue, it seems to me, is not whether the best way to figure out what's going on isn't the consecutive patient registry. It is. The question, it seems, is which devices in this case need to be involved in such an effort, because it's expensive. And the only way this can be done is by industry paying for and following each unit that it sells. You can't be sure that any -- that especially with a device that isn't all that frequently used, that going to two or three centers is going to get you a consecutive patient registry. So I think that's the cure. The question is: How can we in practice apply it? It really is the best way to go with drugs, in terms of defining absolute risk. So you know -- and that's not a problem we're going to solve today, but I think it's something that the FDA has to consider.

DR. PAGE: Point well made.

Dr. Somberg?

DR. SOMBERG: I agree with many of the suggestions that are made, and Bram, to your request for suggestions, one would be, I think, not to depend overly heavily on physicians, but try to go to hospitals and other health givers because a lot of this information is recorded in the hospital. But as said here, physicians don't take the time to report it. When they do, they

often write case reports. And I think that's very important for someone at FDA -- maybe this is done, maybe it isn't done -- to surveill the case report, the literature, the world literature, and to enter that into the reporting system, because I think there's a disconnect for what's reported in the literature and what you have on the -- on the adverse report findings.

And the last thing is I think those down-classified devices, from III to II to I, for a certain period of time, and that's to be discussed, all manufacturing changes should be sent to the FDA, and you should be aware of it so you don't have to depend upon inspectors looking at a file, and if they find that file -- why not have just -- you know, it's not very burdensome to industry to just say, hey, this is the change we made. And then it would be -- you know, you could do with that information as you thought fit. But I'm always impressed by the amount of knowledge at the FDA because you see so much, and each industry, each investigator, we see so little in terms of it. I know the FDA looks upon it the opposite way and you guys have all these resources and everything else, but there's a lot of centrality to this information at the FDA.

So I would just say why not, for this change -- and I can't -- what's it called again, the acronym, the new law change that has really precipitated these type of panel discussions -- why not consider a rule that all down-classifications report manufacturing changes regardless of whether it's minor or serious, because that's always subjective, and whether it's

retrospective or prospective, after a problem, can be very consequential.

DR. PAGE: I'm not going to ask FDA to respond to that specifically, but that's a very good point that you made to them, and I'm sure they'll take that under advisement.

Dr. Jaquiss?

DR. JAQUISS: There is no precedent for registry with devices. The INTERMACS registry is known to most everybody around the table. And I think the INTERMACS registry is a reflection of when it has worked well, which is, for the most part, nice coordination between governmental agencies. And in particular, unfortunately, physicians don't always do what we should. But for the most part, we do what we have to. And the thing that makes us have to do things is the paycheck. So hospital doesn't get paid or a physician doesn't get paid by CMS for putting in a durable ventricular assist device unless they meet certain criteria.

And if one of the criteria for payment were for an ECMO implantation -- were that you entered the ECMO data in a registry which the FDA could have a part in constructing and it would include long-term surveillance and so forth, you know, the TSA was -- you can think about it or not think about it -- but it was formed, in part, in response to a lack of coordination among federal agencies. And I think that your friends at CMS could be persuaded to hold paychecks if people didn't enter into the new ECMO registry for surveillance. That would be a way to get that thing moving

forward. Sounds easy. Probably going to be very difficult, but --

DR. PAGE: Point well made. This is a perfect time for Ms. Timberlake to respond. I saw you taking notes. And I'm very glad.

Dr. Cigarroa, did you have something to amplify before we hear from our Industry Representative?

DR. CIGARROA: Just on the issue of registries, I agree wholeheartedly. I would say, however, that implementation of consecutive series of patients into registries also requires guidance on behalf of education to our hospitals and abstractors as to best practices. I think the INTERMACS data is an example of the potential coupled with the pitfalls of implementation. So --

DR. PAGE: Great. Thank you.

Ms. Timberlake?

MS. TIMBERLAKE: Yes. Sharon Timberlake. I just want to talk a little bit about MDR reporting. It's also important, especially coming from the healthcare facilities and the physicians, that if there is a device malfunction, it's not only reported to FDA, but also to the manufacturers, because we have the best chance of figuring out what that denominator, so to speak, is. When manufacturers receive that information, they look at every single complaint, or they should be. I'm pretty sure they do look at every single complaint and work as teams that involve clinical, medical advisors, R&D teams.

If we make changes, minor changes to the device, typically we do extensive verification/validation questions. Typically, we have a great relationship with FDA, where we can call our advisors at the Agency to get their input as to if we should file a device change, a material change, labeling changes, and very open communication.

So it's not just the physicians, the healthcare facilities, FDA. It's also corresponding back and forth with the device manufacturers. And I'm actually extremely surprised at how many institutions don't report MDRs and then the quality of the MDRs that they do report. It's just -- it's across the board. There's no consistency.

DR. PAGE: Let me just clarify what you're talking about. Were you suggesting that physicians report in addition to an MDR, report individually to industry, and is -- it's hard enough to get one report.

MS. TIMBERLAKE: Right.

DR. PAGE: And are not -- is the information not shared between FDA and industry in terms of our reporting the MDR?

MS. TIMBERLAKE: Sometimes FDA will actually forward a copy of the MDR to the manufacturer. Not in all cases. If you give the information to the manufacturer, they're inclined to report it if it meets the definition for reporting, if it causes serious injury, if the device contributed to the serious injury or the death of the patient. If there was a malfunction but there was no death or serious injury, we still evaluate it to say, okay, is it something

that could happen in the future if the same event occurred?

DR. PAGE: So let me at least give Dr. Zuckerman an opportunity to respond if he cares to, to the suggestion that physicians be reporting both to industry and to the FDA with regard to these issues. If you don't care to comment, that's fine as well, Dr. Zuckerman.

DR. ZUCKERMAN: No, that's fine. Ms. Timberlake was reminding us that with a serious adverse event, hospitals have a requirement to work with industry in terms of filing an MDR report, which eventually goes to FDA. But I can tell you from personal experience that a complementary report also sent by the physician to the FDA separately is often quite helpful for all stakeholders, because it gives a person, a contact, often additional information, often the ability to directly talk about a particular case or cases. And so the more information everyone in this system gets, the better off we all are.

Right now, we have limited information, lack of reporting, and we've heard some good ideas.

DR. PAGE: Thank you. I'm going to suggest that for the next 10 or 15 minutes, if necessary, the Panel focus again on -- I'll get right to you, Dr. Naftel -- focus again on the issues at hand that were presented to us with regard to the reclassification, the risks, safety and effectiveness, and special controls, and just make sure we've had our discussion regarding that, and then for the last few minutes before lunch, actually have whatever discussion

we need about the adult population. And then after we break for lunch, we will reconvene early, but we'll have the open public comment through 1:00 and then go on with the questions. But what I'm suggesting is we finish our discussion with regard to the matters at hand and we have the discussion regarding adults before lunch. Does that work for the Panel?

And, Dr. Naftel, did you have another comment before we proceed?

DR. NAFTEL: Yeah, I'll go very quickly.

Catherine, you said the MDR reporting process was voluntary. I kind of hated to hear you say that, because I'd say the very opposite and you're saying the opposite. There's clear definitions of what's reportable by industry, and they have no choice. There's nothing voluntary. And you're going to correct me if I'm wrong. And then the user facility, also, it's a requirement that the user facility, if the device malfunction resulted in death or injury, they must report it. Now, they treat it as voluntary, but you have very clear regulations. This is not a voluntary database, is it?

MS. WENTZ: I'm going to put this one to Bram because he knows it better than I do.

DR. ZUCKERMAN: Again, Dr. Naftel, from your INTERMACS reporting experience, I think you are pointing to the requirements of manufacturers as to when they need to report an MDR, and you're basically giving us the general drift of required manufacturer reporting, which is an

essential part of the MDR system.

However, it doesn't work, as you know, if hospitals and physicians don't want to be significant players in this system. We have the problem of tremendous underreporting, A. B, I think the point of this discussion was that there's a role for complementary physician independent reporting, which is, in most cases, voluntary but, I would point out to Drs. Yuh and others, can be extremely helpful and critical in terms of putting together a hypothesis when things aren't going well. And let's put it to rest there.

DR. PAGE: Okay. Then at this point, I'd like to just shift our direction and make sure we've had adequate discussion of what was put forward to us today with regard to this reclassification, with these indications, and I'd like to hear from someone just to start off as to their level of comfort and whether we've failed to discuss any important issues.

Dr. Cigarroa?

DR. CIGARROA: Thank you. Again, this is Joaquin Cigarroa. So focusing on the studies identified for indication for use, I think that discussions that were held on the Panel yesterday with regards to the valid scientific evidence are also applicable to today. When we look at the studies reported, only one was a randomized controlled trial. The others are registries or case series with a progressively decreasing amount of information, from the meconium aspiration syndrome to congenital diaphragmatic hernia, to idiopathic primary persistent pulmonary

hypertension, and finally, to the failure to wean, of which there were three case series.

So as we talk about safety and efficacy, I think the context of what is the alternative is very important for the Panel to consider. And I think that's magnified in that last group of failure to wean.

DR. PAGE: So if I may press on, just in the entirety, as per our discussions, you very nicely summarized the issue at hand. We have what we have, and we know the alternatives. Are you expressing some comfort in general to proceed with reclassification as FDA suggested?

DR. CIGARROA: Although I often have internal dissonance, in this case I don't. I am comfortable.

DR. PAGE: I'm glad you're comfortable.

Dr. Borer?

DR. BORER: Yeah. I'm comfortable moving ahead. I would like a little bit more comment really from the Panel members who are pediatric surgeons and pediatricians about the hiatal hernia issue, because that's where it seemed that the data were least definitive because the syndrome is obviously very protean. You know, do you believe that this is a very useful tool in that situation, and are there limitations? Can you describe where it would be and where it wouldn't be?

DR. JAQUISS: This is Jaquiss. I believe it's an effective and useful tool. Before when I sort of sketched very quickly the history of ECMO,

this is a diagnosis where, although it is technically respiratory failure most often, there is also hemodynamic compromise as well. So the comparator group here, the randomized prospective trial model that we all love, doesn't exist. So there really is no alternative. The management of children with congenital diaphragmatic hernias is very much one to avoid ECMO unless you have no choice, and that really is literally having no choice; the patient will die.

There is far from uniform approach to this. Some people put a patient on ECMO who needs to go on ECMO because he or she will die otherwise, and then try to get them off ECMO, and then do the surgery. Other people do the surgery while they're on ECMO. It's a very muddy back of patients to try to analyze, but I don't think there's any -- this is a no alternative population, and I'm satisfied that without ECMO, the mortality rate would be even higher than what we've seen.

DR. PAGE: Dr. Slotwiner, you had a comment?

DR. SLOTWINER: I just concur with what Dr. Cigarroa and Dr. Jaquiss just said. It seems that this technology, while the data may be limited and while it's clearly life sustaining and life saving, it does seem like it can be regulated with special and general controls. And so, as with some of the technology discussed yesterday, I am comfortable with the evidence supporting it.

DR. PAGE: Thank you. Any other comments? Or otherwise,

Dr. Zuckerman, if I may, among the questions that we have later in the day, one of them is to justify the rationale for taking a device that -- reclassifying a device that is life sustaining, and I ask that you consider this discussion, perhaps, when we get to that point later in the day if you're comfortable with that?

DR. ZUCKERMAN: Yes, I am.

DR. PAGE: Great. So if I may now let us shift gears to a more broad discussion to adults, because this is an opportunity. We have some of the world's experts here in terms of regulatory process, in terms of circulatory system devices, as well as pediatric resuscitation and the like. So this is a wonderful opportunity for us to give further guidance. So I'd like to open up the discussion to that issue here before lunch. And the last thing we'll do before lunch during the open discussion period is make sure our Industry, our Consumer, and our Patient Representative have had an opportunity to speak during this discussion period.

So if I may, what else -- what other messages should we be providing the FDA? And let's even discuss and even debate with regard to the potential for expanding the identification or indication for ECMO to adults.

And, Dr. Cigarroa, I'll put you on the spot. I will mention that issues of reimbursement are not within our domain here. So what we're here to do is overall look out for the public good, watch out for identifying risks,

benefits, safety, and then come to at least a recommendation in terms of consideration of an expansion for now not just pediatrics and infants, but adults, in terms of ECMO.

DR. CIGARROA: Thank you. Again, this is Joaquin Cigarroa. I believe that changing the search terms, as we have specifically stated before so that at a future date the FDA can include and report on expanded analysis of the valid scientific evidence that reflects how the device is utilized specifically in the patient population that does not include, or I should say, is not limited to failure to wean. And I think that there are many clinical scenarios in which ECMO can be useful. I think a discussion was held earlier: What are the roles for ECMO as opposed to ventricular assist devices?

And there are a whole host of scenarios in which the utilization of ECMO to provide both pulmonary and circulatory support are important. Left ventricular assist devices, as many people know, can be problematic when the right ventricle is also impacted. So the issue of refractory cardiogenic shock impacting both LV, RV, and the pulmonary circuit, acute fulminant myocarditis, are things that we should look at. The issue of extended cardiopulmonary resuscitation in which there is substantial registry information that has been reported, same registry that the FDA is currently utilizing, and has looked at data, not only the pediatric population, but the adult. So I think those are clear areas that we should look at.

DR. PAGE: Great. And thank you for mentioning a number of

the indications. And earlier on, in response to Dr. Zuckerman, we provided a number of potential indications for adults. You mentioned that it can be useful, and you also mentioned that a literature search needed to be fleshed out more. I'm wondering whether -- and I'm going to be calling on Dr. Somberg here, but if anybody has data that demonstrate utility, not just it's used when there's no other choice, but sometimes there's no other choice. And, for example, the surgeons in the room have all made the decision not to operate when the patient was going to die, right? I mean, every surgeon has had to make that decision. And we as cardiologists go to them and say, please operate, because the patient will die if we don't do surgery, and the surgeon has to tell us, I can do surgery, the patient is still going to die, and I won't do surgery.

So the point I'm making is to expand on data that suggests true utility that you might be aware of. So please respond, Dr. Cigarroa, and Dr. Somberg is up next.

DR. CIGARROA: So there is clear data. And I think it comes down to this issue of the interpretation of valid scientific data and the alternative. So there are substantial single-site reports. There are multicenter U.S. and international registries that reports clinical scenarios in which the technology is implemented, and survival data. So it exists. And I think that the statements that other Panel members have made with regards to the challenge of designing and conducting randomized clinical trials in a

patient population that is moribund with a high probability of mortality are appropriate to consider here with regards to the interpretation of valid scientific data.

DR. PAGE: Fair enough.

Dr. Somberg?

DR. SOMBERG: John Somberg. I think I would second the point that this has to be data driven and that, unfortunately, today we do not have that data before us. Because I'll say this: My recollection of the subject, it was a point of discussion a number of years ago, was that there is a considerable body of data out there. But then again, you can be surprised when you look at it systematically how inadequate it is or how adequate it is. So I'd be loath to just say on the basis of something I can Google now or PubMed and say, hey, this study looks good, maybe that's true or maybe that isn't.

Not meaning to offend anyone, but I've been surprised at the -- my concerns with the data over the last two days. I think we can do a much more systematic review. We should look much more broadly, you know, not say, hey, these are the parameters we looked at. We should look at the parameters we think are best, but we should look at the much more broad literature search. We should not leave unpublished data unmentioned, so other people in the room, whether they be public speakers or members of the Panel, suggest that.

And I believe the charge should be to the epidemiology review group to do their own meta-analysis, a systematic weighted review of the literature at hand, and not say, hey, these are some studies, these are some other studies, we should compare those, we shouldn't compare those. Or defer it to the Cochrane analysis group, and if they are adequate, that is fine.

But I don't think it's up to the individual Panel members to do their own literature review. I think we should all have the same database before us. And I'm an editor of a journal, and we frown now upon just reviews as we used to do them 10, 15 years ago, where you talk about one paper and you talk about another paper. That's no longer valid. Meta-analysis is the way to go, a systematic, weighted, scientific -- statistically scientific, I would say -- approach to the data at hand. And we've not been presented with that material.

DR. PAGE: Thank you, Dr. Somberg. And I'm sure no offense is taken. The Panel and the FDA all understand that we're here to give guidance and express our perspective on what we need to do our job. I'm looking over at Dr. Naftel in case he has any comments.

DR. NAFTEL: Just a quick comment on the other side. The nice thing that FDA has done is you have laid out the exact steps, and it's easy to follow, and therefore, it makes it easy to criticize. But it's a good thing, so we can talk about how to maybe make the search bigger, or whatever. But I want to compliment you for showing us exactly what you've done, and then it

makes it easy to agree or disagree. So I'm rather complimentary.

DR. PAGE: Thank you, Dr. Naftel.

Ms. Timberlake?

MS. TIMBERLAKE: Yes. Sharon Timberlake. I'm going to ask a very direct question, but after you wrap up today, and FDA, you go back and do your homework on the adult population, depending on what those results are, would you feel comfortable including the adult indication within the reclassification?

MS. WENTZ: Yes. That is something that we will take back and we will consider. You know, we've got a lot to consider when we take that back. We need to consider all the regulations and the fact that we brought you here today to discuss what has been cleared, which was just the pediatric and infant patient population. But, again, as we take the actual use of the device into consideration, we will see how that fits in our regulatory boundaries.

DR. ZUCKERMAN: Okay. So Sharon, as Catherine has pointed out, it's a series of steps. But I think where this Panel has been extremely helpful, and I do want to thank the Panel members for this open and rich discussion, is that we do need to take another look at the adult data. And when we do that, we often call upon Panel members to help us out to make the process more efficient and expedited. And I'm sure that we'll be able to get some good help from Panel members here. So I want to indicate that,

number one, we will do the science as to where it will lead. That's always a question mark depending on the data.

DR. PAGE: Thank you, Dr. Zuckerman.

Dr. Lange had a comment?

DR. LANGE: Catherine, so clarify for me, because it's not clear to me, you've three different times where this device is already cleared. So nowhere have I seen what the device is currently cleared for. So help me out.

MS. WENTZ: Okay. Very good question. So the devices that were cleared, as I put up on my slides, were tubing, oxygenator, heat exchangers, and catheters.

DR. LANGE: I'm talking about indications --

MS. WENTZ: Right.

DR. LANGE: -- because we're talking about kids versus adults, and you said it's been -- we're talking about what's been cleared for already. So, and nowhere in here -- and nowhere have I seen that it's just -- it's currently cleared for kids.

MS. WENTZ: Correct. And that's where I was leading to. So none of the labels themselves on any of the cleared devices for long-term use specifically stated for pediatrics or infants and neonates.

However, for example, when you look at the oxygenator, the size of the oxygenator, the data provided in the 510(k) for the long-term

labeling was all for infants and neonates. Bear in mind, also, that the clearance of these devices was quite early and before we really went through things with a fine-toothed comb and had the requirement for the indications for use statement, et cetera. So what we had to take a look at is the device design, how it was designed, and the data that was used to obtain that labeling.

DR. LANGE: So I'm going to bring you back because it's still not clear to me. And I understand the device is a certain size, and you have big people and small people, and some of the small kids are called kids and some of the big people are called kids, too, as a matter of fact, okay? But it's not -- I'm still not -- if I ask you for a piece of paper that said what is this device cleared for, what indications is it cleared for, and the patient population, could the FDA provide me with that? I mean has it --

DR. ZUCKERMAN: In general, no, from a clinical perspective. So let's take a step back, Dr. Lange, because this is a good point for all around the table to consider.

As you know and as pointed out, most of the systems right now are jury-rigged, in fact, the overwhelming majority. And so as Catherine was indicating, the tubing will have the so-called regulatory clearance. It might say that this tubing allows for infusion of blood or something else. But it's not going to give us the big picture, the system picture, with an appropriate clinical label that you would like, ideally. That's one of the reasons why we're

here at this Panel meeting today.

We have a system that has evolved -- I should say a medical system that has evolved such that ECMO is being used in reasonable numbers throughout the U.S. using an off-label system. We here at FDA believe that there is a more appropriate regulatory pathway where we can help identify a good pathway for both product approval and appropriate indications. And that's why your comments going forward as to how we carve out the right indications, what the right data are, what's the interpretation of the data are really essential. And, you know, I would just really try to incentivize the Panel to think about going forward, because the system right now is broken.

DR. PAGE: Dr. Ohman?

DR. OHMAN: Yeah. I wanted to expand on Dr. Lange's comment, because right now, if you took the whole system as it's used right now, there's probably four or five manufacturers for the different components. So this is a clarification for me. The intent of this is to really put it together into one system, and then the question becomes if one company doesn't have all the components, how does, how does this -- I hate to use the word survive, because you know what I'm getting at. If you don't have the cannula, then you can't do the pump, and if you haven't got the pump, you can't do the cannula, so it becomes quite difficult.

So how do you envision this component, or is it more that you get a menu so that you have a menu of things you can pick from?

MS. WENTZ: So that's an excellent question and something obviously that we've discussed at length. And the way that we have proposed the regulation and the identification and the special controls hopefully will give us the flexibility to clear the separate devices. As I stated in one of my slides, we know that, at least as far as I've been at the FDA, for over 20 years, I've never seen an entire system come in. The manufacturers, you know, manufacture a single device. They want to come in with their single device for ECMO labeling. How can we do that? And there's a plethora of data in the ELSO registry for these, at least the indications that we've come up with. And one of the special controls is the in vivo evaluation, which would include retrospective clinical data, and they could potentially use that data in there to get clearance for their specific device.

DR. PAGE: Dr. Balzer?

DR. BALZER: I have more of, I guess, a procedural question or just -- it's probably going to be somewhat controversial, but why is the FDA focused on an indication for use at all in the sense of why specify certain specific indications when, as clinicians, we're allowed to use all these devices off label for whatever indication we think is appropriate. Why not just approve the device as a general tool for cardiopulmonary resuscitation and leave it up to the clinicians?

MS. WENTZ: Because we're data-driven, and we have got to make a decision based on the data that's out there. And right now, we try to

open it up to cardiopulmonary failure in neonates and infants. We gave examples of specific indications, as well as the failure to wean in all pediatric patient populations. The labeling is going to be for the manufacturer to be able to market their device with that labeling as long as they have the data to demonstrate that it's safe and effective for that indication. Like I said, we don't -- we can't do anything about the practice of medicine, and you still have the ability to use the device as you see fit.

DR. PAGE: That was very well said. And, Dr. Balzer, you bring up a very important point. We in the FDA do not regulate the practice of medicine. However, it is our obligation to be satisfied that a device meets adequate safety and effectiveness threshold to then be labeled for that population. And then it's marketed for that population. So while -- when you use a device off-label, which is acceptable and understood by FDA, that's one thing, because in your practice you believe there are adequate data. To be labeled and actually marketed for that use, that needs to reach a higher bar in terms of the data that have been put forward.

One of our concerns today is we haven't seen all the data for adults. So I'm going to bring this back to the indications that were presented to us. Whether it was right or wrong to make the cut there, we can't change that. But FDA felt and I've heard consensus that there were satisfactory data for the pediatric indication. And if we were to approve that, that wouldn't affect the -- it wouldn't be regulating the practice of medicine. It would not

be taking away your decision to use this off-label.

DR. BALZER: I find it interesting, especially as a pediatrician, and I agree, and I understand everything you've said. But virtually everything we do in pediatrics is off-label. So for years -- and we've always had this problem, and they know we've had this problem -- is that we always take adult devices and adapt them for use in pediatrics. It's actually kind of entertaining for me to sit back and see you guys squirm a little bit because the shoe is on the other foot.

DR. PAGE: Turn around. It's fair play.

(Laughter.)

DR. PAGE: Dr. Jaquiss, did you have a comment?

DR. JAQUISS: I'm struggling with this indication thing as well. One of the points that I'd make is -- and I, like Dr. Balzer, am thrilled to see the shoe on the other foot. But the data that have been presented which have been lauded as good and meeting the standards that the FDA wants to be data-driven, we're talking about a system here, ECMO, as though it were some sort of identifiable machine or part. Those data, I guarantee you, that were presented from those studies are not with the ECMO that we use today. We don't use those oxygenators anymore. We simply don't. We have what we think is a better oxygenator, but there are no data that describe practice.

So you're going to be taking a device that was -- you know, has been languishing under whatever regulatory mechanism it's been languishing

under and give that device a reclassification to II, and then ask the adult people -- and to -- based on no data, really. I mean, because the data you used don't reflect this device.

MS. WENTZ: So if I understand you correctly, you're stating that a new device that's on the market that's being used today doesn't have the data in the registry or the clinical data available for us to make that determination?

DR. JAQUISS: This is Dr. Jaquiss. I am absolutely saying that. We do not use the same oxygenator in 2013 in any pediatric center that I'm aware of that was used in the early '90s or in the early 2000s.

MS. WENTZ: Correct. So what my response to that is, is we also, again, in our special controls have a mechanism by which to address that. So if we have a new oxygenator that may not have the data available out there, they will then have to come in with prospective animal and/or clinical data to demonstrate that they are as good as or better than what is currently considered, you know, standard of care and the survival rates that are currently in the registry.

DR. JAQUISS: This is Jaquiss again. So the oxygenator that we currently use now will lose its ability to come to us without bringing you animal data? I don't understand.

MS. WENTZ: So currently you're using these devices as practice of medicine, correct?

DR. JAQUISS: Correct.

MS. WENTZ: Correct. It's not going to change that at all. What it's going to change is if that manufacturer wants to get their labeling for their device for that specific indication, that they are going to have to do a clinical study, a prospective clinical and/or animal study to get the labeling for that indication.

DR. PAGE: And, again, that would be 510(k), not PMA, so a lower bar, but they need to be able to show that the device works together. And actually what this is allowing is actually a regulation which allows you to practice as you see fit, but also gives better comfort to the system being available and tested. And there will indeed be incentive for industry to have their systems evaluated but without going through a full PMA and more randomized trials.

Did I capture that adequately, Dr. Zuckerman?

DR. ZUCKERMAN: You have captured the spirit of the -- in FDA intent perfectly.

Again, Dr. Jaquiss, you know, the practice of medicine is not regulated by FDA. These devices will not be removed from the market tomorrow. We're just looking for an appropriate regulatory pathway which, in best circumstances, will develop more data and better devices.

DR. PAGE: Dr. Cigarroa and Dr. Allen. Then I'm going to ask for very brief comments and discussion, and then I'm going to ask for our

Industry, our Consumer, and our Patient Representatives to speak. If we need to continue this beyond after lunch, we will do so.

Dr. Cigarroa?

DR. CIGARROA: Again, this is Joaquin Cigarroa. Under a query for clarification along the lines of the questions about oxygenators with or without associated pumps to support circulation, I want to come to a statement under the Panel Executive Summary, because I remain confused on this issue. I thought I had it clear, and then I reread this, and I'm confused again. So I'll read this verbatim and ask for clarification.

DR. PAGE: Can you tell us what page you're on for those who have a Panel packet?

DR. CIGARROA: I'm on page 4. So it's under the heading at the bottom of page 3: In summary, the following changes are being recommended for the current classification: Regulation one, renaming the titled of the classification, which is clear; two, redefining and changing the definition and identification of the regulation number, which is clear. From A to B, and it's under the B section that I have, once again, some confusion, such as B, identification: An extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support greater than six hours is a system of devices that provides assisted extracorporeal circulation and physiologic gas exchange of the patient's blood where an acute reversible condition prevents the own body.

So here it links circulation and gas exchange, and I thought that we had earlier today uncoupled the two. But here they appear to be coupled. So I simply want to better understand that.

MS. WENTZ: Okay. So I thought it was clear before. So it's pulmonary and/or cardiopulmonary, not cardiac only.

DR. PAGE: So you're right. That implies they're always linked. But just above it, it clearly states, and elsewhere, it implies that it's pulmonary or cardiopulmonary, not cardiac. But you're absolutely spot on. That's an inconsistency in the paperwork.

Dr. Allen, did you have another comment?

DR. ALLEN: I just wanted to get back to the point about labeling and how important that is. And I think as physicians, we are only beginning to see the tip of the iceberg with how that's going to affect practice. And I've heard more than once now that says the FDA and government doesn't regulate how we practice medicine. But by default, they actually do and increasingly will do so through the reimbursement process. And this is where labeling is so crucial.

And this is why in these types of meetings you want to be completely transparent about how things are labeled because -- two recent examples. When I do a TAVI, if I don't do it exactly the way it is FDA labeled and indicated -- in fact, if I don't even -- if I put it in in a different way, I don't get paid by CMS. Let's look at another expensive device in the same space,

which is VADs. If I put a particular device in that is only approved for bridge to transplant, but I use it in a bridge to decision or a bridge to destination, I don't get paid even though it's approved by a ventricular support device.

DR. PAGE: Your point is well made. I'm going to ask Dr. Zuckerman to comment on to what degree we can be considering the reimbursement issues.

DR. ALLEN: I'm not considering the reimbursement issues, but the point -- we were talking about adults. And my point is that I don't understand, and I want to be transparent about the unintended consequences of decisions that are made that affect one particular population or indication at the expense of another, because that does indirectly affect patient care, and it clearly affects manufacturers.

DR. ZUCKERMAN: Okay. Thank you, Dr. Page, for the opportunity to comment.

As Dr. Page has noted, FDA specifically doesn't look at the economics of medicine, nor does CMS specifically. Their standard is reasonable and necessary, not particularly what the reimbursement is going to be. Be it as it may, though, Dr. Allen is making a very important statement. He wants us, meaning all of the people around the Panel, to consider the whole medical ecosystem, and that's fine because all parts need to mesh together.

But in terms of how FDA can operate in this ecosystem, we are

obliged by our regulations to appropriately label devices, the careful evaluation and determination of whether for particular populations we have appropriate safety and effectiveness data. And, you know, we welcome the Panel's point that we want to have broad, appropriate labeling when possible, and we'll pursue that route, but we also have to recognize what are the FDA rules for appropriate labeling. Thank you.

DR. PAGE: Thank you, Dr. Zuckerman.

We are near the hour of the break, and we are going to break on time. That being said, I don't want to close this session of discussion without the opportunity for our Industry, our Consumer, and our Patient Representatives to make any comments they wish.

Ms. Timberlake, do you have any further comments?

MS. TIMBERLAKE: Sure. I just want to discuss Dr. Allen's point about reimbursement from a manufacturer's perspective. If that's occurring, a manufacturer is going to pursue a 510(k) or a PMA to get that indications for use. I mean, it's a way we survive. If you're not getting paid, you're not using our products, so we'll go back to the drawing board to include that in our labeling. So --

DR. PAGE: Thank you very much.

Ms. Mattivi?

MS. MATTIVI: Kris Mattivi, Consumer Representative. I mean, what a struggle, you know, and what a great discussion and conversation. I

think from the consumer standpoint, I'm certainly concerned with the conversation about not including the adult population in this current discussion and the current labeling indications for use. So I'm pleased that FDA is willing to go back and look at that and consider additional data in that regard. I think that's very important.

As Dr. Allen and Dr. Cigarroa pointed out as well, certainly, reimbursement and liability issues, while not a concern of this Panel, certainly do indirectly affect the practice of medicine and how things are carried out and what kinds of procedures physicians are able to pursue.

So, again, I appreciate FDA's willingness to go back and look at this very critical part of the conversation.

DR. PAGE: Thank you very much.

Dr. Borer, you're raising your hand. Do you have a comment that we need to address before our break?

DR. BORER: We never have to address my comments before any break.

(Laughter.)

DR. BORER: But I think Ms. Mattivi just made the point that I was going to make following up on Keith's point. Forget about reimbursement. The issue of labeling deals directly with liability. If you use a product off-label and something bad happens, you are liable, not the manufacturer. So getting appropriate labeling in place and then really

thinking before you use it another way, so you have all your ducks in order if something happens is extremely important. I applaud the FDA for trying to get this labeling done. I think it's in all of our benefits.

DR. PAGE: Thank you, sir.

Ms. Currier, you have the final word.

MS. CURRIER: Okay. This last 45 minutes has really gotten through to me. I was uncomfortable enough with the data for the pediatrics before we had this discussion. So I couldn't be any more uncomfortable with the adult.

And it could just be because I don't have the medical background. But when I looked at those numbers, you know, I thought, well, you know, these are obviously some very sick kids, and you could see this from how their life went afterwards. But how do you separate whether ECMO is safe from what would have happened anyway. Like, looking at that data, you say, well, the chronic lung disease afterwards, that could have been what they had before, you know, as a result of that. But how do you know from the just plain numbers that you're seeing?

And then I looked at chart 62, I believe, and it showed the ECMO duration and complications. And some of those complications were -- they could be impacting that chronic lung stuff that I worried about. And I thought that there were fairly many complications for the ECMO when I looked at that chart. So the whole thing went like that.

And then now I find out that all this data is being based on -- they're not using that stuff anyway. And so that really troubles me because then I understand all these things about labeling, but in theory, then, they shouldn't be using it.

DR. PAGE: You raised some very good questions, and that's why it's valuable to have a Patient Representative here. We'll do our best to address that after the break, specifically the issues of how ill these patients are and the complications that have occurred. And I think one or more of the physicians can help frame that. But if it's not clear to you, we haven't made it clear enough.

So with that, we are going to move on to break. We will reconvene at 1:00.

Panel members, I ask you to not discuss the meeting topic during the break. This includes discussion among yourselves. Anybody who wants to take their personal belongings, please do so. We will be securing this room during the break.

We'll call the meeting back to order promptly at 1:00, when we will have the open public hearing. And then we'll proceed with any final discussion and then go through the questions posed by the FDA. So we're adjourned until 1. Thank you.

(Whereupon, a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

DR. PAGE: I'd like to resume this meeting of the Circulatory System Devices Panel.

We are now going to proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to discuss -- to address the Panel, to present data, information, or views relevant to the meeting agenda.

Ms. Waterhouse will now read the Open Public Hearing disclosure process statement.

MS. WATERHOUSE: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the

Committee if you do not have any such a financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. PAGE: Thank you very much. We've had two requests to speak. Each speaker will be given 10 minutes to address the Panel. When you approach the lectern, please be sure to state your name, company, and any affiliation you may have with the entities presenting today. We have a light system which will show you green for nine minutes and yellow for one minute, and you're given 10 minutes to speak.

And our first speaker is William Bolt, Senior Vice President, Global Product Operations for Abiomed, Incorporated. Welcome, Mr. Bolt.

MR. BOLT: Thank you. Get the slides up?

DR. PAGE: We are not holding you accountable for the time for us getting these slides going.

MR. BOLT: I'm afraid to touch it.

(Laughter.)

MR. BOLT: Thank you. And I just hit down? Forward? Okay.

Thank you for letting me speak today. My name is Bill Bolt, and I'm the Senior Vice President of Global Product Operations for Abiomed in Danvers, Massachusetts. We're a device company, 33 years old, that has been focused on the area of circulatory support and ventricular assist all that time. I'm a full-time employee for the last 31 years, and they paid my travel

here today and my meals and everything else.

So part of my role at Abiomed is managing the regulatory function. And in that context, Abiomed is here today to support the FDA position of recommending that ECMO use in adult cardiac failure patients remain a Class III designation. This is for two reasons.

The first is that FDA recently held a 515(i) panel meeting in December of 2012 on non-roller-type bypass pumps, which several physicians on this Panel participated in. The purpose of this meeting was to assess if the preamendment classification of Class III was appropriate for all devices cleared under this category.

In the meeting, the FDA proposed a new use or indication for a subgroup of these pumps, titled temporary ventricular support. In their presentation, they endorsed that certain devices, including ECMO, remain in Class III, and the FDA Panel agreed with their recommendation.

The second reason is that there are devices approved that serve the population of adult cardiac failure. All have been approved through the PMA process in our Class III devices.

The next slide contains FDA slide 77 that was shown by FDA at the December 515(i) panel meeting for the non-roller-type pumps. You can see on the left of the slide ECMO is represented as one of the devices used for temporary ventricular support. This category shown in this slide, as recommended by the Panel that day, was to remain Class III.

The next slide shows four devices. They were all approved for adult cardiac failure indications under PMA, starting from over 20 years ago, the BVS 5000 from Abiomed, later the PVAD from Thoratec, and finally, the AB 5000 from Abiomed and the IVAD from Thoratec, are all labeled as biventricular devices addressing patients in cardiac failure. All of these devices were approved through the PMA process.

The next slide shows specific intended uses of the Abiomed devices, the AB 5000. Please just refer to the underlined indications so it's easier to read. But the patient indications include failure to wean, failed transplant, right ventricular failure on patients that have an LVAD in place, and myocarditis as examples.

The next slide shows that the Thoratec device labeling also covers bridge to transplant and, again, another option for failure to wean indication.

So, in conclusion, the regulatory classification for ECMO in adult cardiac failure should remain as Class III. This is for two reasons. First, the recent December 515(i) Panel recommendation to FDA was to maintain a Class III for ECMO when intended for use in temporary ventricular support.

Secondly, there is a long history of devices used for treating patients with adult cardiac failure indications. All are Class III devices, and the regulatory pathway for approval was under the PMA process. Both are consistent with FDA's positions on recommending a Class III designation for

ECMO in adult cardiac failure, and Abiomed supports this.

Thank you.

DR. PAGE: Thank you very much.

We'll proceed with the next speaker and then open up the discussion for any questions from the Panel for either of the speakers.

The next speaker is Sammy Almashat, Dr. Sammy Almashat, researcher from the Health Research Group. Welcome.

DR. ALMASHAT: Thank you. My name is Sammy Almashat, a physician with Public Citizen's Health Research Group. I have no conflicts of interest.

Public Citizen strongly urges the Food and Drug Administration to withdraw its dangerous proposal to reclassify ECMO devices from their current Class III for two indications.

ECMO devices must remain categorized as Class III devices for all indications because they are life sustaining devices for which clinical trials or at least some human data are necessary to provide reasonable assurance of safety and effectiveness and reasonable assurance of substantial equivalence. If the trials conducted to date are deemed sufficient to provide such assurance, why does the FDA not formally review these data as part of premarket approval applications consistent with the device's current Class III designation?

And the most important point, in our view, that may be lost in

the discussion on the safety and effectiveness of current ECMO devices is that the decision today to down-regulate ECMO devices from Class III to Class II for these two indications is primarily important and has implications for future ECMO variance, ECMO variance that have not yet been developed. And this, I think, is the most important point that needs to be considered.

The recent issue with the metal-on-metal hip implants demonstrates this. The decision in the 1970s to effectively not require PMAs for future metal-on-metal hip implants resulted in the recent removal from the market of the variant -- of the new variant of metal-on-metal hip implant that was approved based on substantial equivalence. And I think that case more than any other highlights the deficiencies of the 510(k) process as applied in the real world.

When the FDA has to assess these devices that involved dozens or hundreds of components based on data that is not from clinical trials, they have to determine clinical relevance based on non-clinical data. We think that is fundamentally problematic.

The two indications for which the FDA is proposing Class II designation are in situations where imminent death is threatened by cardiopulmonary failure in neonates and infants and where cardiopulmonary failure results in the inability to wean from cardiopulmonary bypass following surgery in pediatric patients. For one of these indications, there have been no randomized controlled trials supporting the efficacy and safety of ECMO

therapy in pediatric patients who fail to wean from cardiopulmonary bypass. And I'll come back to this a little later.

There is sufficient evidence, and we agree that there is sufficient evidence, demonstrating safety and effectiveness for increase in survival in neonates with severe respiratory failure based on randomized controlled trials conducted in the 1980s and '90s. However, it does not follow that this evidence for effectiveness in neonates should necessarily result in downgrading approval requirements for this device and future variants. If the FDA has deemed the evidence sufficient to determine efficacy and safety for this indication, this should be reviewed as part of the PMA submission.

The central question is not whether any of the previously tested versions of the device were safe and effective, but whether moving forward the FDA can reasonably be assured of the safety and effectiveness of new ECMO devices without requiring data from well-controlled clinical trials.

Given that ECMO devices are intended for life sustaining indications in patients in critical condition, even minor but therapeutically significant changes in the structure or functionality of the device could potentially mean the difference between life and death for a patient. It is precisely for this reason that ECMO and other similarly life-sustaining and life-supporting devices have traditionally been designated as Class III devices.

In response to an earlier letter we sent the FDA urging Class III

designation for all indications, the FDA responded that if different types of safety and effectiveness questions are raised based on the technological differences between a new device and an older device, the newly designed device would be ineligible for the 510(k) process and be a Class III device, requiring a premarket approval application.

However, this reasoning begs the question: How will the Agency know whether technological differences raise clinically relevant safety or efficacy questions if no clinical trials or human data are required comparing the newer to the older version?

The history of the evidence for ECMO devices in adults with ARDS is a case in point. In the 1970s, a large randomized controlled trial in adults with severe respiratory failure comparing ECMO devices with the conventional treatments at the time was terminated early due to futility. More than 90% of patients died despite the treatments, with no significant difference in mortality between the arms.

A subsequent 1994 trial also failed to demonstrate any benefit of ECMO therapy compared with conventional therapy in adults with ARDS. It was not until the publication of the CESAR trial in 2009 that efficacy was demonstrated, though with serious limitations, as were discussed today, the major limitation being that 1 in 5 patients assigned to ECMO never received ECMO, yet still did better than the control group.

It stands to reason that different design features of the ECMO

versions tested in each trial were at least partly responsible for the markedly different trial results. Therefore, we ask again, absent required clinical trials or -- controlled or not controlled, how will the FDA provide reasonable assurance that future ECMO versions will be as safe and effective as current models?

The FDA points out correctly that, in some instances, such as failure to wean from cardiopulmonary bypass, where medical therapy has failed, controlled clinical trials would not be possible or ethical given the inability to used failed medical therapy or nothing as a control. We agree that such studies would be patently unethical, but these are not the only type of trials that could be required under a PMA.

An example are the case series that currently are serving as the basis for the FDA's proposed reclassification for pediatric patients who fail to wean from cardiopulmonary bypass.

A non-inferiority trial comparing a newer ECMO version to an existing version is precisely the sort of clinical data that would guarantee or at least provide some reassurance that the newer device is substantially equivalent to existing therapy. And no ethical barrier of the sort identified by the FDA exists for such trials.

Another concern centers on the lack of robust evidence for ECMO in adults and the off-label issue. An unintended but clearly foreseeable consequence of the down-classification of ECMO devices to Class

II for some indications is the increased potential for off-label use for other Class III indications. With the possibility of clearance through the 510(k) pathway made possible by a Class II designation for one indication, few ECMO device manufacturers will likely pursue expensive clinical trials to support Class III approval for additional indications if the device can readily be used as it is now, off-label for these indications without clinical data. This will likely result in the continued problem of off-label use of ECMO devices for the remaining and any future Class III indications without safety and efficacy data.

This is a critical reason that life-supporting and life-sustaining devices such as ECMOs should always remain as Class III for all indications. It is for these reasons that we urge the FDA to withdraw its proposal for Class II designation and to issue a final rule maintaining Class III designation for these devices, requiring PMA submissions for all indications.

Thank you.

DR. PAGE: Thank you. I want to thank both the speakers for concise and clear presentations to the Panel.

Does anyone else wish to address the Panel at this time? If so, please come forward to the lectern and state your name, affiliation, and indicate your financial interest.

I'm seeing no one.

Does the Panel have any questions for the Open Public Hearing

Speakers?

Dr. Borer?

DR. BORER: Yes. Really for the last speaker, I tend to agree that some kind of in vivo data should be available as new devices are considered for the indications we're discussing. But I've just looked back at the special controls that were suggested by the FDA, and bullets 4 and 5 say just exactly that, in vivo evaluation of the device, which obviously could be in animals according to that bullet. And in vivo evaluation of the device must demonstrate device performance. And the next bullet is labeling must include a detailed summary of the non-clinical and clinical evaluations pertinent to the use.

So would that not meet the concern that you have for these devices if these special controls were used rather than mandating new trials or new observational studies beyond this?

DR. ALMASHAT: Right. And I think our point is that if the in vivo data applied exclusively to human data and to robust human data, and we're not necessarily talking about trials involving thousands of patients, which are always a challenge with devices, as opposed to drugs, but what we are saying is that given the complexity of these and other devices, such as metal-on-metal hip implants, given the absence of a discrete active ingredient that you can identify and determine bioequivalence, as is the case with drugs, it becomes more important to evaluate the device in human

patients, such as a non-inferiority trial with an existing device in order to provide reassurance of substantial equivalence that the FDA is currently using as the basis for a 510(k) approval.

You know, why -- what -- our question is what is gained by today's down-classification of current ECMO devices to a 510(k) threshold. You know, if the data are sufficient, which we believe they are for neonates, why not formally review this under a PMA with similar requirement for future variants. Again, the metal-on-metal hip implants, no one foresaw that minor modifications to the structure of the devices would result in vastly different clinical outcomes because there were no human trials. And that is precisely the point that we are making.

So if the in vivo data were to -- if the FDA were to require human data as opposed to animal data and robust human data and have some standards for that human data, then we would certainly agree with that.

DR. PAGE: Thank you.

Dr. Ohman, did you have another question, again, for the speakers? This is not time for discussion, but questions for the speakers?

DR. OHMAN: Yeah. I have a few, if you don't mind, sir. I have just a question just on a sort of technical issue, but you said that you recommend non-inferiority trials. Now, as you know, those require certain margins to be predefined for, so obviously you thought through this. So I

would be interested in sort of what non-inferiority margin you might consider to be a valuable number in this setting.

DR. ALMASHAT: So that's always a challenge of non-inferiority trials, is determining the line between inferiority and non-inferiority. Is 10% worse non-inferior or is 15% worse non-inferior? And to my knowledge, what's used at CDER for drugs is a 15% margin. Now, while that's not perfect, we think that it is more reassuring than vague determinations of substantial equivalence under the 510(k) pathway. We think an imperfect non-inferiority trial is better than a -- than, you know, a non-standardized threshold for substantial equivalence that could be applied.

DR. OHMAN: So my question, then, would be 15% --

DR. ALMASHAT: Again, I'm not going to -- honestly, I really don't know --

DR. OHMAN: IS that very -- it's out of the air, right? It's a complicated field.

DR. ALMASHAT: Well, this would be something that the FDA would determine, but all we're saying is we're not recommending details here. We're recommending the principle that, you know, substantial equivalence should rest on human data when it involves structural changes to a device. And the FDA has not answered the question to our satisfaction of how they will determine whether a device, a new device, is substantially equivalent to an older device in terms of clinically significant outcomes if

there is no clinical data.

DR. PAGE: Was there another question for the speakers from the Panel?

DR. ZUCKERMAN: No, Dr. Page. I'd like to make a comment after this part is finished and before we go onto the next part.

DR. PAGE: I welcome that. Right now we're in the Open Public Hearing section, and I'm looking for a question from Dr. Somberg, again, for one of the speakers.

Dr. Somberg?

DR. SOMBERG: Yes. This is for the gentleman from the -- who was just talking here.

DR. PAGE: And, again, for the record, Dr. Almashat -- did I say that correctly?

DR. ALMASHAT: Yes.

DR. SOMBERG: Dr. Almashat.

DR. PAGE: Thank you.

DR. SOMBERG: I'm sorry. I don't have that name. Were you and your organization objecting to the down-classification for ECMO devices overall or in the pediatric, because you seem to have gone back and forth of talking about the pediatric indication is -- or there's more information, more evidence, and you were giving examples from the adult area. So can you clarify that point for me?

DR. ALMASHAT: We are against down-classification for the pediatric indications, including the indication for which robust clinical data aren't present for safety and efficacy. And the reason for this is that medical devices, obviously, are modified over time. And the decision on down-classification is most relevant for future ECMO variants. And it is for this reason that we think that if the evidence is sufficient for the pediatric and the neonatal population, there is no reason why that should not be reviewed under the formal PMA process and not under the 510(k) process.

DR. PAGE: Are there any further questions for the speakers?

(No response.)

DR. PAGE: Seeing none, I want to thank both you and Mr. Bolt for very clear presentations, and I now pronounce this portion of Open Public Hearing to be officially closed.

We will now proceed with today's agenda. The plan for this afternoon was for us to respond to Ms. Currier's very good questions and concerns that she raised.

And I'd ask Dr. Lange to kind of summarize from a physician's standpoint the good point -- the good questions you raised, being our Patient Representative. And then following that, we'll proceed with deliberations as needed before going on to addressing the FDA question as they've been provided to us.

But Dr. Lange?

DR. LANGE: And appreciate your comments as a Consumer and as a Patient Representative as well.

I'll address primarily two comments. One is how poorly individuals do that have received ECMO therapy. And just to put it in perspective, as our surgical colleagues alluded to earlier, these are devices that are usually put in as a very last choice of treatment, those individuals have failed medical therapy, and there really is no other therapy thought to be available to sustain their life either for a reversible condition that they can get over or to bridge them to a more definitive therapy. And so it's sobering that the patients do not do very well, but absent this, the thought is, as my colleagues mentioned, is they would die.

The other issue was the issue of the changing device. And that's actually, from a medical standpoint, we consider that a plus. These devices continue to improve. They continue to improve with their manufacturing process, with their safety. The industry takes whatever the current use is and troubleshoots to find out what problems are occurring and how to make that so it's safer for the patient and it's more effective as well. And this is a therapy that has matured. And so what I would say is that even though the oxygenators are different than they were five or six years ago, it is, again, an industry that has matured, and the devices are actually better, presumed to be better. That's why we're doing it. And the industry doesn't take two steps back and give you a worse device.

And one of the things that the FDA is charged with doing is making sure that we do apply these things effectively to the right patients and that the therapy is thought to be safe and effective, and that any changes or any modulations are, in fact, improvements, and we can prove that. So I hope that addresses your -- the issues.

DR. PAGE: Thank you, Dr. Lange.

Ms. Currier, do you have any further questions?

MS. CURRIER: No, I just wanted to say something to the --

DR. PAGE: Yes, please.

MS. CURRIER: Thank you very much. And the thing that -- I guess my comment about the data, you know, given that they're using different things that -- is not -- I mean, I understand that there's all sorts of off-label things being used, but the excuse for not -- or reason -- not excuse -- reason for not doing adults was the data was not that good. And then when you look at it, the data for pediatric can't be that good either because it's all based on a different device. Do you see what I'm saying? That was my point.

DR. LANGE: Yes -- no, I think your point's well taken. Part of it is device. Part of it is the types of trials. We consider the gold standard to be a randomized controlled trial, where a patient could receive treatment A or B, and the test is, is B better than A. And circumstances like this, where the only option is death, where you say, you're going to get a device or we're

going to just withdraw therapy, we don't have the opportunity to perform randomized controlled trials. Almost everything is a series or matching studies. And that's true for what I tried to -- what I pointed out to the FDA is that the trials that we're talking about with kids are case series. And what they're going to look at in adults are case series as well. And it's the best available data.

As you know, yesterday -- what the FDA does is look at the totality of data, randomized controlled trials, human experience, case series, observation, and then our experts as well. And I applaud the FDA for looking at in toto.

MS. CURRIER: Thank you.

DR. PAGE: Thank you.

Dr. Somberg, did you have a comment?

DR. SOMBERG: Yeah. I just wanted to say you have to balance things. You have to balance things out in that you're saying they didn't do so well in the pediatric population because you listed a lot of problems, and there even is delayed mortality, but that's compared to almost certain early mortality.

MS. CURRIER: Right.

DR. SOMBERG: So there's always this question, and it's a question many of us face in practice of medicine is you can help somebody, but you can't always change the complete course of events. And while you're

not making someone whole and perfect again, you know, how much have you helped and how much you haven't. And in some areas -- that's why a lot of us have gone into cardiology -- in some areas, we can help a lot more than in other areas. And I'm not going to condemn my colleagues in other fields. I won't mention their names. But this is a much better field.

So I think you should take home the messages that when you looked at the data, yes, there's all sorts of these side effects, all sorts of adverse reactions. And there's a lot of adversities that are disease-related, not necessarily treatment-related, but that pales in comparison to the alternative, which is not being around.

MS. CURRIER: Thank you.

DR. PAGE: Thank you, Dr. Somberg.

Ms. Currier, could you please turn off your microphone unless you want to speak?

And, Dr. Cigarroa, did you have another comment on this specific topic? Thank you. Go ahead.

DR. CIGARROA: With regards to the equipment with which the case series and randomized controlled trials were performed in contrast with what is currently being utilized, part of our responsibility here today is to address the issue of special controls. And so I think that will help potentially uncover any likelihood of unintended consequences of design refinement.

DR. PAGE: Thank you, Dr. Cigarroa.

I'd like to now resume the Panel deliberations that began this morning. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. In addition, we request that all persons who are asked to speak to identify themselves each time. This helps the transcriptionist identify the speakers.

So we've already had a robust discussion of the matter at hand, and I believe we've agreed that when we go into the questions, we're going to be specifically addressing the questions as they were put to us with the indications that were put forward by the FDA before this Panel met.

We've had discussions about the issue of adults. And when we get to Question 4, I'm going to ask for each individual to weigh in on classification. But I'd also like a comment briefly about the adult question. But beyond that, we're going to limit our discussion when we go through the questions to the matter that was put at hand to us.

So if I may just start off, are there any further comments or deliberation we should undertake with regard to the -- what was put forward to us in the first place?

And, Dr. Zuckerman, do you have a comment?

DR. ZUCKERMAN: Yeah, unless -- well, let me begin first. First, I want to just thank the two speakers who have just spoken. They did an outstanding job, again, in terms of really outlining the landscape, giving hopefully all you Panel members additional food for thought. But I think

before you go into this critical section, I'd like to remind you of several key points.

One is, you know, you just heard some considerations of this class or that class, but for the last 35 years, even though ECMO is technically a Class III device, these devices have been evaluated through the 510(k) program. One.

Two is that there was just a good discussion on needed clinical data. Regardless of whether it's a 510(k) or a PMA, if the FDA believes for an appropriate evaluation clinical data are needed, then the FDA will obtain clinical data before making an approval decision. And I just want to assure you of this point, because Ms. Catherine Wentz, you know, pointed this out before. It's often a point of confusion between PMAs and 510(k)s. Forget about that distinction. When the FDA needs clinical data, it gets clinical data before we sign off on things.

Finally, there was a good mention of the fact that, unfortunately, while we would like absolute device safety, we can run into problems. The example was given of the metal-on-metal hips, which is a significant problem. And when we run into problems, we have panels just like this convene. And if we need to upregulate and change our regulatory strategy, then we're more than willing to do it. In fact, for the metal-on-metal hip situation, there has been a call for PMAs due to the nature and seriousness of the problem.

Thank you.

DR. PAGE: Thank you, Dr. Zuckerman.

Now let's resume with the Panel deliberations. I've already heard -- Dr. Allen?

DR. ALLEN: So over lunch, as I pondered this and the discussion going back and forth between adult and pediatric and how they interact, I had some clarity. And I'll borrow from Dr. Zuckerman, and I'll step back one or two steps.

And I like to put things in buckets. And as I think about this now, and the FDA can correct me if I'm wrong, but the way I look at this and the way I maybe see a simple way of looking at this is to think about devices that, for example, if you have somebody in cardiogenic shock and you place them on an ECMO device, while they may be on an ECMO device, it's really a VAD. It's a VAD with an oxygenator in it, but they probably don't even need the oxygenator.

If you put somebody on a ECMO device after cardiopulmonary bypass, you're doing it because it's easy to do and less expensive than a formal VAD, but you're really doing it because you want a VAD. Has nothing to do with the pulmonary aspect that we're talking about. And that's very different than the indications that we're talking about in the pediatric population, because all of those, for the most part, are driven by pulmonary issues. There is some hemodynamic issues with diaphragmatic problems, and

the failure to wean from bypass isn't an oxygenation problem. It's typically a pump problem. But you don't have VADs, and so ECMO is what you have, and that's the toy you use.

So I feel even more comfortable after kind of thinking about that, that, you know, adult ECMO really is very complicated, and we generically use the word ECMO to describe what maybe isn't really ECMO. It's really just another form of ventricular assist device, and that's already covered in a separate way by the FDA.

Is that perhaps the way you're thinking about it, Catherine or John?

MS. WENTZ: Yes, thank you. Once again, you provided clarity --

DR. PAGE: Microphone, please?

MS. WENTZ: -- to the situation. Turn your -- I think -- there you go. So thank you. Yes. Once again, you've provided clarity to the situation.

That said, there may be some instances in adult care that would require ECMO and is pulmonary-driven that we could take a look at, as suggested before. But I think you've captured it very well. Thank you.

DR. PAGE: Dr. Lange?

DR. LANGE: I guess I ate lunch differently.

(Laughter.)

DR. LANGE: Okay. And while I would agree with you is that

oftentimes, they're used in circumstances for circulatory support, it's very different than putting an LVAD in, and you know more about -- a lot more about that than I do. And I think it's important that the FDA, as they've agreed to do, to look at the data with regard to adults for both long injury, alveolar hemorrhage, lung transplant, proteinosis, cystic fibrosis, those kinds of things, and for cardiac support as well, because I think its uses can be very different, and sometimes used as a bridge to get someone to a destination, so --

DR. PAGE: Dr. Allen?

DR. ALLEN: Just as a response, I totally agree with that, but once again, most of what you were talking about is pulmonary-driven. It's pulmonary support. And I think that's the distinction. So cystic fibrosis, lung transplant, all of those things are related to the oxygenator being a key component of this circuit. And whereas a lot of what we talk about with cardiac support has nothing to do with pulmonary insufficiency. It's simply supporting the ventricles.

DR. LANGE: And so I should say, in addition to those things, it's used in adults for myocarditis, cardiomyopathy, cardiogenic shock, post-failure to wean, and then especially for CPR as well, where it's getting increasing use.

DR. ALLEN: Those are -- but once again, and I don't want to belittle the point, but those are all cardiac support where you're using it as a

VAD, as a ventricular assist device. You're not using it as an ECMO device to provide oxygen to the patient.

DR. PAGE: Dr. Somberg, did you have a comment?

DR. SOMBERG: Yeah. Well, I think devices, if they're down-classified, are cleared for marketing. It's not their specific indications and the pathophysiology behind it. So you're not saying, well, it's an ECMO device, but I'm using it as a VAD, or I'm using -- it's an ECMO device, I'm using it as ECMO. We're talking about a manufacturer that comes with a specific product. And the question, I think, is whether that product will have to go through a PMA clinical trial process or by special controls.

And I just want to emphasize, I don't think we should discuss the adult population today because we haven't had the data presented to us. And everybody is at a different level of knowledge, and the level of knowledge may not be up to it. But I say, I do say it should have been, and we should have had that material, but we don't. So we can't discuss it today. And I'm not, you know, prepared -- you know, we heard, well, you know, maybe in ARDS it doesn't work, but maybe here it does, or maybe it does and what's the level of evidence. I don't think that's certainly appropriate.

I also want to make one other distinction. Our representative in the audience from Public Citizen who was talking about needing clinical data -- and I think what Dr. Zuckerman said is so critically important. Clinical data is different in a PMA process with clinical trials for evaluation of efficacy

and safety. And I think that's a big distinction. And while different devices come in, the device approval system is such that we accept small iterations of changes hopefully for their improvement to be cleared by special controls. And it's very distinct from having a completely separate indication and having needing for a PMA.

So just saying, hey, we need a clinical trial for everything, well, gee whiz, that' s a tremendous use of resources. And there's only so many patients and so many studies you can do. So you have to decide where a clinical trial is. So I would say if someone comes up with a novel use for ECMO in a special population, that's going to probably need a clinical trial. But if it's in this rubric of pediatrics, there's a wealth of data here, and maybe some clinical evidence, some safety determinations are needed, but that's distinctly different. And in the adults, we just have to find the evidence, and that has to be a rigorous review, because I think there are several hundred papers out there. And I don't think anyone here has all those in their hand and knows the pros and cons.

DR. PAGE: Thank you, Dr. Somberg.

Any other comments at this time, or are we ready to move on to the questions?

(No response.)

DR. PAGE: Looks like we are ready to move on. I should mention for the audience that our plan is not to have a break, but to move

forward. So in that setting, at this time, let us focus our discussion on the FDA questions. Copies of the questions are in your folders. I want to remind the Panel that this is a deliberation period among the Panel members only. Our task at hand is to answer the FDA questions based on the data in the Panel packs, the presentations we've heard this morning and this afternoon, and the expertise around the table. With this said, I would ask that each Panel member identify him or herself each time he or she speaks to facilitate transcription.

And, Ms. Wentz, would you please read the first question for us?

MS. WENTZ: Okay. So now for the questions.

Question No. 1: FDA has identified the following risks to health for extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support, based on the input of the prior classification panels, review of industry responses to the 2009 515(i) order, the Manufacturer and User facility Device Experience, or MAUDE, database, and FDA's literature review.

The following risks to health have been identified:

- Thrombocytopenia;
- Hemolysis;
- Adverse tissue reaction;
- Inadequate gas exchange;

- Gas embolism;
- Mechanical failure;
- Hemorrhage;
- Hemodilution;
- Thrombosis or thromboembolism;
- Infection; and
- Mechanical injury to access vessels.

Question to the Panel is this: Is this a complete and accurate list of the risks to health presented by extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support? Please comment on whether you disagree with the inclusion of any of these risks or whether you believe any other risk should be included in the overall risk assessment.

DR. PAGE: So I'll open it up to the Panel. Anybody care to comment? Is this list of risks sufficient? Is it complete and appropriate?

Dr. Jaquiss?

DR. JAQUISS: At the risk of scaring Ms. Currier even more, I think it's incomplete. I don't see any specific mention of renal dysfunction, kidney injury, kidney dysfunction, which is a well-known complication of initiation of cardiopulmonary bypass or ECMO. I also don't see any discussion specifically of neurologic injury, which is certainly probably the biggest issue faced in the pediatric, particularly neonatal population.

There are two other more subtle kind of picky points. And one

of them is that you've discussed specifically thrombocytopenia. I think more broadly, a disorder of the coagulation, fibrinolytic system, which sometimes is called disseminated intravascular coagulation, or DIC, is a fairly frequent event certainly in children and probably in adults, as well, on ECMO, and that maybe ought to be covered in more broad language.

And it's a little bit difficult to explain, and I'll do my best, but there is a growing recognition in clinical medicine that transfusion is bad for you. There is a lot of deleterious consequences of transfusion. And some of those are long-term in that they sensitize people against foreign antigens, which make transplantation much more difficult. And some of them are more subtle and more acute in terms of immunosuppression. But just bleeding in and of itself is something that you can die from or that can be viewed as a complication, and I think we can all understand. But receiving a transfusion is also inherently a bad thing, and ECMO makes it more likely that you will receive a transfusion.

DR. PAGE: Thank you. As Ms. Wentz is setting up, I think, a slide for her response, we yesterday had quite a discussion about the distinction between risks and adverse events related to the potential risk of the device. And I'm hoping FDA can further clarify on that specific issue. But you raised some very important points. And let's -- do you want to respond, Ms. Wentz?

MS. WENTZ: I would love to, but I can't find the slide.

DR. ZUCKERMAN: Okay. But Catherine, regardless of the slide --

MS. WENTZ: Right.

DR. ZUCKERMAN: -- I think Dr. Page has made a critical point. Would you like to respond or do you want me?

MS. WENTZ: There it is. I do have the slide. So as we did have discussions yesterday, there is a distinction between the term risk to health and adverse event. So, for example, you mentioned neuro injury. At a previous Panel meeting, death was considered as a risk to health. We would categorize those as adverse events. So, for example, a risk to health is more a direct risk associated with the use of the device itself. An adverse event would be a consequence of that risk. So, for example, as up here, the risk to health identified as inadequate gas exchange could conclude as an adverse event hypoxemia. Thromboembolism could conclude as death. So there's a fine line there between risk to health and adverse event. So that taken into consideration, would you then revise your list?

DR. PAGE: Please use the mike.

DR. JAQUISS: This is Jaquiss. You've introduced a level of sophistication that I'm about going to stumble with, and I think I'd rather not do that in public.

DR. PAGE: But I would actually -- I think you're giving too much credit. The level of sophistication is also a bit of confusion. It's an important

issue that you bring forward, that while these are regulatory terms, as Panelists, as physicians, as a caregiver, no matter what you call it, you don't want renal failure and you don't want death, and you don't want neurologic injury. So I think it's an important message for FDA to hear, and I appreciate you raising that question. I've seen Dr. Cigarroa, Dr. Allen, and Ms. Timberlake.

Dr. Cigarroa?

DR. CIGARROA: I believe there is data, and correct me if I'm wrong, that there is initiation of a systemic inflammatory response which, in fact, may lead to some of the adverse effects that I think you have importantly highlighted. So I would include that. I think that falls along the category of what you're listing here.

DR. PAGE: Thank you.

MS. WENTZ: So can you restate that? What would the risk to health be that you'd like to add?

DR. CIGARROA: Activation of inflammatory pathways, and whether that's under the heading of adverse tissue reaction or not --

MS. WENTZ: Yes, that's exactly what it would be.

DR. CIGARROA: Okay.

MS. WENTZ: Thank you.

DR. PAGE: Dr. Allen, did you have a comment?

DR. ALLEN: Yeah. While I think those are all very good

complications and adverse events, I think that the list is, quite honestly, quite comprehensive. So things like thromboembolism takes care of the adverse event of cerebral vascular accident, you know, bleeding or hemorrhage takes care of a intracranial bleed. And you can go down the list. So it's a nuance. You have to go to law school, I think, to understand it or have heard it multiple times, but there is a method in their madness.

DR. PAGE: Thank you.

Ms. Timberlake, did you have a comment?

MS. TIMBERLAKE: Yes. I just want to point out, the list of adverse events that you bring up, that'll end up being in the labeling based on either literature or prospective studies, whatever the Agency decides to get the device on the market.

DR. PAGE: Dr. Ohman?

DR. OHMAN: I should know this, but I don't. In the risks and -- not risks, not adverse events -- whatever this list is --

DR. PAGE: These are risks.

DR. OHMAN: Is the regular cardiopulmonary bypass that -- I guess I wasn't part of that meeting, but that was in the fall, I believe, is this list the same or is there something additional on that list that is not there, such as non-pulsatile flow?

MS. WENTZ: So the meeting in December was for pumps, not for oxygenators. And I have not compared the list there with here. The

specific risks to health for the pump as compared to the risks to health that we've identified for an entire ECMO circuit. I think that they are all-inclusive. We gave a lot of thought to this. So I think they are. But I will check.

DR. OHMAN: Thank you.

DR. PAGE: So I'm going to make an attempt at summarizing the Panel's perspective on this, Dr. Zuckerman.

With regard to Question 1, the Panel generally believes that the list of risks is appropriate, with the understanding that adverse events may result from these risks. I do wonder whether adverse tissue reaction really captures an inflammatory response, so I'd just have you consider that as to whether that represents an individual risk, because I would not have intuitively thought that would encompass that.

But, Dr. Zuckerman, is this adequate?

DR. ZUCKERMAN: Yes. Thank you.

DR. PAGE: Thank you very much. We'll move on to Question 2.

Ms. Wentz, would you please read that?

MS. WENTZ: Question 2: As defined in 21 C.F.R. 860.7(d)(1), there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from the use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. As defined in 21 C.F.R. 860.7(e)(1), there is

reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

The FDA believes that available scientific evidence supports an adequate assurance of safety and effectiveness for extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support where imminent death is threatened by respiratory failure (for example, meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension) in neonates and infants, or cardiorespiratory failure (resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery) in pediatric patients.

Questions to the Panel are:

2a. Do you agree that the available scientific evidence is adequate to support the safety and effectiveness for extracorporeal circuit and accessories for long-term pulmonary/ cardiopulmonary support when used as intended; and

2b. Do the probable benefits to health from use of the extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support outweigh the probable risks to health when used as intended?

DR. PAGE: Thank you very much.

May I ask the Panelists to comment on Question No. 2?

DR. REICH: I would say that the answer to 2a is yes, and the answer to 2b is yes.

DR. PAGE: Thank you very much.

I'm looking around at a bunch of nodding heads. Dr. Naftel?

DR. NAFTEL: So I'm going to say yes and yes, but I still trip over the words, and I'm sure you get tired of me saying this. But, you know, if you had a young couple with a one-month-old baby and they're faced with death, and you say, okay, we're going to put in an ECMO circuit in, and they go to the FDA website, everybody goes to the internet, and they say, thank God, this thing is safe and effective, we're home free. You know, it's safe and effective. Thank God. Well, of course that's not the way it's defined and not the way it's posed, but man, I hate these words. I just do, because it's not safe. It's better -- the risk/benefit -- and that's the way it's defined -- the risk/benefit is right, but the words are just so unfriendly.

And then a second point, and then I'll be quiet, we haven't discussed at all long-term outcome after ECMO, you know, if there's stroke, if there's severe brain damage, if yes, the patient's alive but not doing well. We had a little bit of discussion, but we haven't -- we've kind of ignored that, and we focused on survival and not the state of the patient, and I worry about that. But I still vote yes and yes.

DR. PAGE: Is there anybody who wants to comment on Dr. Naftel's raising the issue of long-term? Obviously, the data we've seen are not long-term in general, although we've heard of some follow-up at seven years for the randomized trial.

Dr. Borer?

DR. BORER: Yeah. Though I certainly share Dr. Naftel's concern, I think that, you know, the data are the data, and seven years is a pretty long time. It's at least a bridge to something if there ever is a something.

But I would like to get back to his earlier comment. I agree with the concern about the wording, but I understand it in a slightly different way, and you know, perhaps it's something that the FDA can consider. I think that the device is effective and acceptably safe for the intended use, which actually deals with the issue of relative benefit -- the relation between benefit and risk. You know, as we've all said, no drug, no device is absolutely safe. And none, unfortunately, is absolutely effective. But I think that it's -- and the words are in there. It's just not phrased exactly that way, acceptably safe for the intended use.

DR. PAGE: Ms. Timberlake?

MS. TIMBERLAKE: Yes, I just want to point out about the comment on the long-term studies. You have to keep in mind, as a device manufacturer, where the device is intended in use, and when that patient

goes home, they don't go home with continued use of the ECMO system. So therefore, one, it's hard to hold a manufacturer responsible for including long-term studies in order to seek marketing approval. And, two, I think it's a hard design based on there's so many other confounding issues within that patient that could cause you concerns. I'm not saying that it's not a worthy study that needs to be conducted. It's just more of a matter of it's not so much the responsibility of the manufacturer to include that in a study design to seek FDA clearance or approval.

DR. PAGE: Thank you for providing that viewpoint.

Dr. Zuckerman, I would say that with regard to Question 2, the Panel generally believes the answer is in the affirmative to both of these. As with every Panel that I have ever sat on, there is discomfort if you just take the individual word safe and effective. That's why there is a paragraph around each of those words. But when the FDA can come up with a better way of describing what we're getting at here, we would welcome that. But in the meantime, with the definitions as they're provided to us, the Panel is comfortable in the affirmative for Question 2a and 2b.

Is that adequate for you?

DR. ZUCKERMAN: Yes. Thank you.

DR. PAGE: Thank you. We'll move on to Question 3, please.

Ms. Wentz?

MS. WENTZ: Question 3: The FDA believes that a reasonable

assurance of safety and effectiveness for extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support is available when indicated for use in conditions where imminent death is threatened by respiratory failure (for example, meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension) in neonates and infants, or cardiorespiratory failure (resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery) in all pediatric patients. FDA believes that the following special controls can be established to adequately mitigate the risks to health for extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support.

Special controls include:

1. The design characteristics of the device must ensure that the geometry and design parameters are consistent with the intended use;
2. The devices must be demonstrated to be biocompatible;
3. Sterility and shelf-life testing must demonstrate the sterility of patient-contacting components and the shelf-life of these components;
4. Non-clinical performance evaluation of the device must demonstrate substantial equivalence in terms of safety and effectiveness for performance characteristics on the bench, mechanical integrity, EMC (where applicable), software, durability,

and reliability, et cetera;

5. In vivo evaluation of the device must demonstrate device performance over the intended duration of use and for the specific indication; and
6. Labeling must include a detailed summary of the non-clinical and clinical evaluations pertinent to the use of the device and adequate instructions with respect to anticoagulation, circuit set up and maintenance during a procedure.

Questions to the Panel:

Question 3a: Please comment on whether these special controls are adequate to mitigate the risks to health for extracorporeal circuit and accessories for long-term pulmonary/ cardiopulmonary support when used as intended and provide sufficient evidence of safety and effectiveness.

Question 3b: Please comment on whether you disagree with inclusion of any of these special controls or whether you believe any other special controls are necessary.

DR. PAGE: Thank you very much. Before we proceed with the Panel's discussion of Questions 3a and 3b, may I just ask for clarification, for the record, in terms of slide 89 -- I guess it's your 90 -- and bullet one, in vivo evaluation of the device. You mentioned earlier that that could be inclusive of clinical data if seen as necessary; is that correct?

MS. WENTZ: Correct.

DR. PAGE: Okay. With that, let me open this to the Panel to comment on Question 3.

Dr. Yuh?

DR. YUH: Yes, thank you. In general, I do agree with the special controls, though I think in this particular case when you're trying to consolidate all the different components with the ECMO circuit, that compatibility should be included in the non-clinical performance parameters. I don't see that on that listing. I see mechanical, durability and reliability, and so forth, but I think compatibility in this case might be particularly important since you may be mixing and matching several different components.

MS. WENTZ: So you mean compatibility with respect to the other components, not biocompatibility --

DR. YUH: The other components.

MS. WENTZ: Yes --

DR. YUH: Right, right. And then the second question I might have is since complications are associated with duration of use, that the intended duration of use specified in one of these criteria be more specific. It's a rhetorical question. Do we need to be more specific since complications are known to be associated, at least linearly, with the duration of use?

MS. WENTZ: So, historically, what we've done is we clear or approve devices based on the data that they've given us, so if they can

demonstrate for us clinically and on the bench that they can work for two weeks, that's the labeling that they get. If you all feel as a Panel that the clinical outcomes significantly drop after two weeks on ECMO, we may consider a cutoff.

DR. PAGE: I guess I'll ask Dr. Yuh, if you're still on ECMO at two weeks, no matter what it's labeled for, what would you do if the patient still needs ECMO?

DR. YUH: I mean, I'd keep it going, but I think that -- at least I hope so -- you know, again, it was a rhetorical question. I only ask it because it's pertinent to the known risks of the use of the device.

DR. PAGE: But I think you raise a very important issue, and that is, clearly, the complications increase with longer use. So as soon as it would no longer be necessary, it should no longer be implied? Is that what you would say?

DR. YUH: Yes.

DR. PAGE: Great. Thank you.

Dr. Naftel?

DR. NAFTEL: One question. With these controls, I think, these are the minimum controls? And if you had a new device that came along and it really looked like it was a bit of a change, could you impose a postapproval study if you wanted to on the new device in addition to these controls?

MS. WENTZ: And Bram may correct me if I'm wrong, but since

we don't have it listed here, no, we couldn't, but we could include that as a special control?

DR. ZUCKERMAN: Okay. Let's take a step back. I think where Dr. Naftel is going is we're trying to define a certain device type that's pretty standard, and the special controls would be used. But if a really unique 22nd-century device comes in or one with significant modifications, Catherine and her team go through the standard 510(k) flowchart. And I think where you're going, Dr. Naftel, is that that device would be booted up into the PMA category, where the ability to do just what you said is part and parcel of the PMA review process.

DR. PAGE: Thank you.

Dr. Balzer?

DR. BALZER: This gets back to Dr. Yuh's point before, but I'm still a little bit concerned because this isn't a single device; it's components. So if an individual device manufacturer comes with a new piece of tubing or a new roller pump, and that looks equivalent to previous ones, at the end of it all, it gets put together in a single machine, and then who's actually going to be responsible -- I mean, ultimately, you guys are -- for the oversight of that device and how they're all going to work together, because the individual manufacturers are not going to do that?

MS. WENTZ: It's being done right now, isn't it? They're putting them all together right now.

DR. BALZER: Well, they're putting them all together, but then who's going to make sure that if there's problems down the road, that somebody is actually looking at is it a compatibility issue? How is that resolved?

MS. WENTZ: So the MDRs is -- the MDR reports are one mechanism that we can use to take a look at any of those -- those types of adverse events. The compatibility issues with the circuit components is a good one and something that we will consider in what needs to be provided in the labeling for these devices, for example, the pressures that the device can withstand or the -- you know, specifications like that would have to be spelled out in their labeling so that you couldn't use an oxygenator or a heat exchanger together if their pressures do not -- are not compatible.

DR. PAGE: But if I'm correct, if this goes forward as submitted, the entire circuit would be put forward in a 510(k). So the entire circuit fitting together would be evaluated by FDA in anticipation, is that right?

MS. WENTZ: Not entirely. So again, like I said, we have not completely vetted out the process by which we are going to clear new devices. But I'm going to give you an example of what we have discussed.

So the standard of care indications that we have discussed right here, lots of data in the ELSO registry. Lots of devices have been used for these indications. If this goes through and the final order reclassifies these indications, I'm anticipating many 510(k)s to get this labeling. The docs

can then use the devices that have the labeling and put together a circuit, an ECMO circuit. It may be different from hospital to hospital because we'll have several different components that are going to have that labeling. So it's not going to be one circuit that's going to be cleared. And we tried to build that flexibility in because of the way devices are manufactured.

DR. PAGE: So if I may just follow up, in terms of the -- when a device is put forward, do you still see an oxygenator, for example, coming forward alone or as part of a circuit, whether it's from that own company's devices being put together or using others?

MS. WENTZ: Generally, what we've seen is they come forward alone because we don't -- I have never seen a 510(k) for an entire circuit. I've seen them for all the individual components, not for an entire circuit.

DR. PAGE: And you would anticipate that that would be the case if this regulation goes through that we're discussing today?

MS. WENTZ: Yes. Now, with the caveat also that devices are improving and are being combined, and we now have oxygenator-pump combination-type devices. So they are getting smaller, where we're actually reviewing several devices as one.

DR. PAGE: Dr. Zuckerman?

DR. ZUCKERMAN: Okay. To provide the Panel with a little bit more clarity -- and this may be where Dr. Page was going. He can comment also. Suppose a new oxygenator comes in that wants this particular label.

When you do all the preclinical required bench testing, the circuit that it's tested with and some of the parameters need to be fairly standard for what its conditions of use would be in the real world. Can you describe how the preclinical testing would be relevant such that when it is cleared, it could be used for a variety of ECMO jury-rigged circuits?

MS. WENTZ: So for the case of a new type -- a new device that doesn't have the data or is not cleared for bypass and does not have the long-term data that may be in the ELSO registry, we do have the bench testing. A lot of the bench testing is acute. You can't do long-term blood studies. The long-term testing for bench studies would include the reliability and durability testing for the device, and that would be performed under the parameters that you would see in the clinical environment. And we usually make them do twice the intended duration of use just for the added assurance that it will be used -- that it will be safe for those two weeks or one week or whatever they want their labeling for.

Regarding the clinical component -- so if this is a new device, we would most likely need animal and/or clinical data as the in vivo part of the special controls. And what we would do there, again, assuming if this reclassification goes through, we receive these 510(k)s for the devices that have been on the market and have the clinical data retrospectively in the registry. They get the labeling. If we get a new device, that device could be used in a circuit of devices that already has the labeling. So you'd have a

control with a circuit that already has the labeling, and then you'd have your test circuit with those same devices with the one device removed and the new one put in. And you could run a clinical study that way.

DR. PAGE: That's much more clear.

Are there any other comments with regard to Question No. 3 on special controls?

Ms. Timberlake?

MS. TIMBERLAKE: I just want to comment on your concern about looking at it as a system from a manufacturer's perspective. Typically, when we file a 510(k), and I've done multiple with many different devices, including our own, we evaluate the product as a whole. We look at the risk analysis as a whole. And we also do validation testing with what's most typical out there used by physicians and typically recommend, if it's another manufacturer's device or a generic naming for it -- for, like, trocars, for example, we'll have physicians call us and ask if they could use our device in a different sized trocar. We have to look and see if we validated it, if it can support that type of use. So from a manufacturer's perspective, we do look at that. If there's changes where the other manufacturer does implement something that could affect our system, so to speak, we then go back and we do validate it.

DR. PAGE: Thank you.

So if I may summarize, Dr. Zuckerman, with regard to Question

No. 3, generally the Panel felt that the list of special controls was adequate and appropriate, although compatibility, not biocompatibility, but compatibility of the components would need to be assured and evaluated. The issue of duration of use is a complicated one in that -- but at least needs to be considered. And, again, issues of what is being put forward and how it fits into the circuit is something that there is at least some concern that these -- again, getting back to compatibility of these devices, would be an important special control. Is that satisfactory, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, it is. Thank you.

DR. PAGE: Thank you. So now we're moving on to our final question, Question 4.

And, Ms. Wentz, would you please read this to the Panel?

MS. WENTZ: Sure. Question 4: 21 C.F.R. 860.93 described the classification of implants, life-supporting or life-sustaining devices and states that "the classification panel will recommend classification into Class III of any implant or life-supporting or life-sustaining device unless the panel determines that such classification is not necessary to provide reasonable assurance of these of the safety and effectiveness of the device. If the panel recommends classification or reclassification of such a device into a class other than Class III, it shall set forth in its recommendation the reasons for so doing..."

FDA believes that extracorporeal circuit and accessories for

long-term pulmonary/cardiopulmonary support are life supporting, which was supported by the original classification panel for membrane lung for long-term pulmonary support. However, FDA believes that the risks to health for extracorporeal circuit and accessories for long-term pulmonary/ cardiopulmonary support can be mitigated with special controls, in conjunction with general controls, and therefore recommends that these devices be reclassified as Class II devices.

Questions to the Panel:

Question 4a: Do you agree that extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support are life supporting?

Question 4b: Based on the available scientific evidence and proposed special controls, what classification do you recommend for extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support where imminent death is threatened by respiratory failure (for example, meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension) in neonates and infants, or cardiorespiratory failure (resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery) in all pediatric patients.

And Question 4c: In accordance with 860.93, if you recommend a

classification other than Class III for any of these indications, please discuss the reasons for your recommendation.

DR. PAGE: Thank you very much.

Dr. Somberg had a clarifying question, perhaps?

DR. SOMBERG: Exactly. You said earlier, to your knowledge, the devices that are out there were for pediatric use. And I just wanted you to reconfirm that. And the other side of the coin is that if the Panel recommended down-classification for this group of devices only for pediatric, the result would be, given the legal framework, I believe, is that you would have to issue a final statement on the adult use of these devices either to call for a PMA or to down-classify them or they would be misbranded and have to be taken off the market if they were used for that.

So right now, all that stuff is irrelevant, from my understanding of your statement, because everything that has gone through the FDA is for pediatric use. Is that correct? And I'm sorry to give you such a difficult question. You look like you're under some duress --

MS. WENTZ: No, it's a very good question, and I think as we brought up before, the indications that were cleared were very broad and did not specify adults or pediatric patients. Basically, it said what the device did. It was a tool indication.

Based on the data that we have in the files themselves and what was used to support the long-term use labeling, it was indicated for

pediatrics and neonates. Now, that said, obviously, it's used for adults off-label. So the 515(i) process, we are supposed to discuss what was cleared and put into Class I, Class II, or Class III, those indications, those devices that have been cleared. We have not cleared any adult-indicated devices for ECMO. So we are not doing a split reclassification.

DR. SOMBERG: I hear you. But specifically, is there a device, a component of a device out there that, by its obvious size and volume, would raise a red flag and therefore initiate a process calling for a PMA or a removal of that component or device from the market. And I think that -- and the reason -- I'll give you time to think about that, because the reason I think that's important is it affects how we deliberate in this remaining time whether it is germane to start discussing the pediatric versus adult and the difference, and whether the evidence base is there or not, et cetera, because it's not going to initiate that process. But if it does and it limits the practice of medicine, that is of concern to many people in the clinical realm.

DR. ZUCKERMAN: Okay. So, Dr. Somberg, thanks for that additional clarification. And I think the intent of your question is to assure or to ask FDA if FDA moves in a certain direction that could affect adult availability of ECMO, what does FDA do? And so let's again take a step back.

We always make decisions very carefully, especially regulatory decisions of very complex and life-saving devices. So if there were an instance where we would make a regulatory decision that, taken upon face

value, would remove an important therapy for adults, we would pause and consider how we can also make sure that we don't adversely affect the public health of this nation. And, you know, in a prior reclass Panel, we got into a discussion with ADs whereby we could appropriately take regulatory action and not take devices off the market for a period of time. The same type of regulatory discretion and thinking about public health would be utilized here, I can assure you. So instead of asking Ms. Wentz to, you know, frantically look for a possibility, I think your comment is extremely well taken, and it's part of the public record.

DR. PAGE: Thank you, Dr. Zuckerman.

So I'm going to frame our discussion for Question No. 4 in that context. And if I may summarize, we have been presented data with regard to pediatrics, the indications that were brought forward. And there's been concern raised by the Panel that we have not had the opportunity, and indeed we have not had a full opportunity, to review adult data. And we have at the same time, I think, given good guidance to FDA in terms of the need to fully vet the data for adults.

But for Question No. 4, we're here to respond to the three questions put forward as they're put forward for the indications that we're here to discuss today. I'm going to take the prerogative of assuming that everyone here agrees that Question 4a is affirmative. These are life supporting.

So if I don't see any shakes of the head, and I'm seeing nods, we're just dealing with Questions 4b and c. I'd like someone to speak up and comment on (b) and (c); (b) is where you would put the classification, whether you would advocate for reclassification to Class II, and to speak to how you justify that as per (c).

Once we've gone through that, we don't all need to repeat the same comments, but any new comments are welcomed. I will ask for everyone to speak up. This is not a voting panel, but this is a panel where I would like to at least hear from everyone who's willing their suggestion in terms of reclassification.

The final thing I'll ask is as you are speaking to Questions (b) and (c), if you have any other comment with regard to the adult issue, without going into length, we've discussed that at a fair amount of length, but I would like to hear any further comments with regard to adults, again, not answering (b) or (c), but making sure everyone is on the record as having an opportunity to speak.

So with that, Dr. Zuckerman?

DR. ZUCKERMAN: Yeah, Dr. Page, thank you so much for bringing up the adult issue again. I want to emphasize to the Panel that that part of the discussion up to now has been extremely fruitful for FDA. And, consequently, in consideration of this question, it would be extremely helpful for Panel members to be quite vocal on both the pediatric and adult

populations regardless of your recommendations.

DR. PAGE: Thank you very much.

So I'm seeing Dr. Cigarroa?

DR. CIGARROA: So with regards to Question 4b, for pediatric patients as indicated, I believe the answer is yes.

With regards to 4b as it relates to adults, I believe that it is imperative as the Panel and the FDA move forward that we have an opportunity to adequately look at the clinical data that exists in order to address that aspect which I don't think we were able to cover today, but we highlighted the importance and the clinical need to do so in a regulatory environment.

In regards to 4c, I believe that down-classification from III to II is reasonable and that the special controls that have been delineated by the FDA are sufficient.

DR. PAGE: Thank you very much for your responses and your justification for your responses.

So at this point, I'd look for others to comment and give a straw vote, if you'd like. Again, I'm not asking for a vote on adults, because on adults, we can't come to a conclusion. I feel strongly we can't come to a conclusion as to how it should be regulated, but a comment, if anyone cares to, further about how we might proceed in terms of the adults in the future.

Dr. Slotwiner?

DR. SLOTWINER: Thank you. And I can't summarize it better than Dr. Cigarroa. But, in addition, I think as the speaker from Abiomed pointed out, I think the information, the data for adults will be important to consider that in the context of the previous Panel's deliberations as well as the data. So I think that does deserve to be considered separately.

And one more point about why I think it will be helpful to down-classify to II, as mentioned earlier, but I just want to reiterate, I think that this will allow more vendors to actually follow through and seek the labeled indication, which I think will improve the quality and labeling.

DR. PAGE: Thank you very much. So you were in favor of reclassifying to II?

DR. SLOTWINER: Correct.

DR. PAGE: Yes, Dr. Jaquiss?

DR. JAQUISS: I apologize for asking what, to me, was a very basic question up front. You said repeatedly that you have cleared some devices through existing pathways for ECMO, and you mentioned tubing cannulas and I think oxygenator, and I can't remember whether you mentioned pump. Do you know specifically which oxygenator, and you have not done a pump?

MS. WENTZ: Have not done a pump. The oxygenator was the original SciMed oxygenator, which I think Medtronic now owns.

DR. JAQUISS: I would point out, I think as I did earlier -- this is

Jaquiss again -- that that, in effect, means that what we're proposing to do here is to down-regulate a device which is no longer used clinically, and then even -- so what we're using now would have to go through the 510(k). That said, I'd be in favor of doing that.

And my comment about the adult data is that I believe that a compelling case can be made in favor of the adult data now. It hasn't been done. It wasn't done. But I think it can be done, and I strongly urge that this Panel or one like it be convened fairly quickly. And the FDA should perhaps seek additional input from adult ECMO-logists, of which I am not one.

DR. PAGE: Thank you very much.

(Laughter.)

DR. PAGE: Dr. Naftel?

DR. NAFTEL: So I vote or comment that it should be downgraded to Class II --

DR. PAGE: May I just ask just for clarification. I'm concerned about down-classification and downgraded. We are reclassifying, and I hope, appropriately, if you are voting for a change from III to II or maintenance of III, that you emphasize you think this is the right regulatory process for the device. Sorry to cut you off.

DR. NAFTEL: Thank you. And that actually was exactly my comment, exactly, because I'm looking at what Marjorie gave us this morning, and to get to Class II, it's sufficient information for special controls.

We're a little bit headed, I think, to Class II because we don't think a randomized trial is possible, we don't see any other way to do this other than through the special controls. So the point I would like to make is exactly the point you made, that we're no way saying that we're there, there's no more information to collect, you know, we're in good shape, we know what we're doing. We're not doing that at all. We're just saying this is the best regulatory process for an important device.

DR. PAGE: Thank you so much.

If I may, let's just go down the table with the panelists to just let us hear your voice in terms of the question at hand. And, Dr. Borer, I don't think we've heard from you yet.

DR. BORER: I would say yes, yes, and yes, and that there should be some effort to more completely assess the use of the devices in adults to determine whether there is a good basis for reclassifying.

DR. PAGE: Thank you.

Dr. Reich?

DR. REICH: I vote yes, to reclassify it to Class II. My reason is because the definition we were given is when there's adequate knowledge base and special controls can be established to adequately mitigate the risks to health, a Class II recommendation is appropriate, and I think that that is true.

And as far as adult data goes, I don't know. I don't take care of

adults.

DR. PAGE: Thank you, sir.

Dr. Lange?

DR. LANGE: Well, you're going to hate me for this, all right? But if imminent death is threatened, I actually like that, right? You want the threat of imminent death, I think we ought to -- but if imminent death is threatened, I wouldn't put one of these in.

(Laughter.)

DR. LANGE: You get my drift, Catherine?

MS. WENTZ: Yes.

DR. LANGE: Otherwise, I totally agree in the reclassification.

DR. PAGE: Thank you, Dr. Lange, I think.

Dr. Ohman?

DR. OHMAN: So I also agree for the pediatric population that (b) is affirmative and (c) is recommending for use of Class II for the pediatric population.

For the adult population -- let me back up. One thing on the pediatric, I would like to see some way of understanding within the construct of this new environment of putting a whole system together with all the tools and all the bits and pieces, that we actually have some sort of menu that it is clear to different manufacturers where they fit in, because it's not clear to us, I don't think, at this point, as we use all of these devices differently.

As far as the adult population, I can't comment, because we haven't seen much of the information. I do believe that we do need to have a classification of the conditions that will be applicable for this use. And then, under (c), it would be unknown because we don't have enough sufficient information to date.

DR. PAGE: Thank you.

Dr. Yuh?

DR. YUH: Yes. I'm in favor of reclassifying to the Class II, although the compatibility issue still gives me some pause. When you think about it, if you're considering the whole circuit comprised of even just four components, the combinatorial possibilities are significant; if I'm not mistaken, if it's four components, 24 conceivable different combinations. But I'm confident in the FDA's ability through the 510 pathway to safeguard that. I think, essentially, for all intents and purposes, from a regulatory standpoint, it's already a Class II device. You're evaluating new devices in that sphere along the 510(k) pathway. So with that in place, the data in the pediatric population is comforting with respect to its -- with its current use. So I am again in favor of reclassifying.

In terms of the adult application, I, like the others, would be more comfortable in seeing the data presented in a more formal environment and manner to really comment on it.

DR. PAGE: Dr. Somberg?

DR. SOMBERG: I concur with my colleagues. I think, as I've expressed, my criteria for down-classification -- not downgrading -- that's what the airline does to me -- but down-classification is that it -- that there is adequate information in the field to support the appropriate balance between efficacy and safety and that it doesn't interfere critically, does not interfere with the performance of clinical trials and the expansion of knowledge. You know, if it's really questionable and we need more information, then we should favor the PMA route. In this case, I do not believe that's the case. I believe there is substantial evidence in this area. It's very adequate.

The other critical component is do we have adequate ability to have special controls for a Class II device, and I think that's been agreed to by most everybody on the Panel. So I think we have met the criteria. It is appropriate.

As regarding adults, I think that needs to be addressed in a future panel, as other people have said, and my only other point to add to that is that I really think we have to try to be as scientific and systematic as we can, and we should use -- and I'm advocating FDA perform a meta-analysis of the trials, giving them appropriate weights. Obviously, a randomized controlled trial with 1,000 patients on the topic at hand is better than 10,000 patients in, you know, an observational, non-controlled, open-label study. So with appropriate tools of meta-analysis, we can really look very critically at

that data. And I don't think it has been looked at in that way, and this may be pioneering both regulatory work and science.

DR. PAGE: Thank you, Dr. Somberg.

We've heard from Dr. Jaquiss. Dr. Balzer?

DR. BALZER: I'm just going to reiterate what I think most people have said already and more from the department of redundancy department. But, basically, I would favor reclassification to Class II for the pediatric indications for the reasons that have already been specified, in terms of general and specific controls. And I'll have to reserve judgment on the adult comment since I'm not familiar with the literature.

DR. PAGE: Thank you.

Dr. Cigarroa? Actually, we've heard from you already --

DR. CIGARROA: I already commented. I just want to change --

DR. PAGE: Dr. Allen?

DR. CIGARROA: -- change the statement to reclassification.

(Laughter.)

DR. PAGE: Thank you, Dr. Cigarroa.

Dr. Allen?

DR. ALLEN: So I also would concur, as I've said earlier, with reclassification to a Class II device. I think the risk can easily be mitigated with special controls.

With regard to adults, I think that needs to be looked into. As

you think about it, it may be much more complex than we in the Panel first gave our -- gave it thought to, and maybe some advice might be to split things between VV ECMO and AV ECMO. VV ECMO more closely mimics what we're voting on right now, which is pure pulmonary support, versus AV ECMO, which cobbles together both cardiopulmonary support as well as actually VAD therapy.

DR. PAGE: Thank you very much.

So Dr. Zuckerman, with regard to Question No. 4, I heard unanimity of the expert panel in terms of concurrence with Questions 4a and b, that indeed this is life supporting and that there was comfort in reclassification to Class II.

The issue of adults has been discussed, and you've heard from the Panel perhaps a desire to have had a full -- a more full review of the adult data. You've commented that, from the FDA standpoint, at least to the degree that things were looked at before this Panel, there would be a welcoming of increased data. And obviously randomized controlled trials are not realistic, but the better data or sufficient data to look at this in terms of adults would be desirable. In the meantime, there's been a call for potentially another panel. I'm not sure -- you'll have to tell us whether that's necessary or whether this could be taken on through the FDA itself.

Is that an adequate response from your standpoint?

DR. ZUCKERMAN: Yes. That's very well done, Dr. Page. And I

want to thank the Panel members for their very thoughtful responses on this particular question.

DR. PAGE: Thank you.

We're not quite done yet because we are privileged to have representatives from industry, consumers, and patients. And I'd like to first ask Ms. Timberlake, our Industry Representative, for any additional comments.

MS. TIMBERLAKE: Sure. From an Industry Rep's perspective, as well as a mother's perspective, looking at it in a peds environment, obviously, death versus clearing the device through the reclassification obviously makes sense.

In the scope of looking at it from the adult perspective of indicating it as whether it's a Class II or a Class III, as you evolve through this process, I just ask that you communicate often with members of industry so they have a sense of where your heads are, if they can help with any of the literature, call meetings, pre-IDE meetings to get their input so when you do make a decision, there's not lengthy delays for industry, as whether they have to go forward with a 510(k) or a prospective study to support a 510(k) or a PMA.

DR. PAGE: Thank you very much.

Ms. Mattivi?

MS. MATTIVI: So, also, I would like to thank the Panel and the

FDA for a very stimulating, intellectual discussion. From the standpoint of a mother of a 16-year-old male who just got his driver's license, I may perhaps have considered another option when he was born, but, yeah, I don't know. But, you know, to reiterate my previous comments, I do think the topic of addressing this issue for the adult population, and I applaud the FDA for their openness in reconsidering that information. And I'm looking for the consumer being well served by ongoing communication between the manufacturing community and the FDA.

DR. PAGE: Thank you very much.

Ms. Currier?

MS. CURRIER: Well, Dr. Naftel really threw me for a loop because now you have the old wordsmith sitting here worrying about safe and effective. I wish somehow the labeling could say "better than the alternative," because that's really the way I feel about it, you know? So I would agree with reclassifying it, but just not because it's safe and effective, but it's better than the alternative.

And with the adult, I would hope that the FDA would move as quickly as possible on that. You know, I look at the timeline for this reclassification and I worry about the adult. Thank you.

DR. PAGE: Thank you very much.

And I want to point out how much we all appreciate your representing patients, Ms. Mattivi in terms of consumers and Ms. Timberlake

likewise for industry. You really enhance our ability to get our job done.

And I also want to thank the FDA for a very nice presentation and the Panel for what has been a lively discussion.

I also want to just thank the public comment speakers. I think it's of interest that both industry and the group representing the public both actually came down on the same side in actually suggesting that we not reclassify. And I can speak on behalf of the Committee that we take your comments very seriously. At the same time, in our deliberation, we believe we're doing the best for the public and the common good by establishing or recommending the classification as we have. But we do take your comments very seriously, and we very much appreciate the public comment.

With that, Dr. Zuckerman, do you have any final remarks?

DR. ZUCKERMAN: No. I just want to thank Dr. Page and the rest of the Panel for an excellent day's work. The comments that we received are quite important, and we will use them in our subsequent decisions.

Thank you.

DR. PAGE: Thank you very much.

Given that, the September 12th meeting of the Circulatory System Devices Panel is now adjourned. Have a good evening.

(Whereupon, at 2:43 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

CIRCULATORY SYSTEM DEVICES PANEL MEETING

September 12, 2013

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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